Online supplementary material S3: Details of included studies

Contents

Abbreviations

AS	Ankylosing spondylitis
CBT	Cognitive behavioural therapy
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
axSpA	Axial spondyloarthritis
SSc	Systemic sclerosis
SS	Sjogren's syndrome
IA	Inflammatory arthritis
AE	Adverse events
SAE	Serious adverse events
CI	Confidence interval
OR	Odds ratio
VAS	Visual analogue scale

Alten et al., 2011	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=277) ≈ Female 82% ≈ Age, years: Canakinumab 150 mg SC q4wk: 57.1, Canakinumab 300 mg SC q2wk: 61, Canakinumab 300 mg SC q2wk + 600 mg IV loading dose: 55.6, placebo: 57.5 ≈ Disease duration, years: Canakinumab 150 mg SC q4wk: 11.1, Canakinumab 300 mg SC q2wk: 10.1, Canakinumab 300 mg SC q2wk + 600 mg IV loading dose: 9.8, placebo: 8.8 Revised 1987 ACR classification criteria
Intervention(s)	Canakinumab: canakinumab 150 mg subcutaneously (SC) every 4 weeks (q4wk), canakinumab 300 mg SC (2 injections of 150 mg SC) every 2 weeks (q2wk) or a 600 mg IV loading dose of canakinumab followed by 300 mg SC q2wk
Intervention(s) characteristics	Canakinumab is a fully human anti-IL-1beta monoclonal antibody with a plasma half-life of 3-4 weeks that selectively neutralizes the bioactivity of IL-1beta. Patients were randomized in a double-blind fashion to receive one of the following four possible treatments in addition to methotrexate over 12 weeks. The canakinumab doses were selected based on the results of a previous dose-escalation, proof-of-concept study in patients with active RA despite maximum tolerated doses of methotrexate, as well as on pharmacokinetic/pharmacodynamic modeling.
Control	Placebo q2wk
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Compared to the placebo group, all three canakinumab treatment groups exhibited trends toward greater improvement in FACIT-F. Differences vs. placebo in LS mean change (95% CI) in canakinumab 150 mg SC q4wk, canakinumab 300 mg SC q2wk, and canakinumab 300 mg SC q2wk + 600 mg IV loading dose were 4.4 (1.3 to 7.5), 2.5 (-0.7 to 5.6), and 3.5 (0.4 to 6.7), respectively. Compared to placebo, significantly greater improvement in FACIT-F scores was observed with canakinumab 150 mg SC q4wk, and the 600 mg IV loading dose plus 300 mg SC q2wk.
Safety results	The proportion of patients who experienced at least one AE was 52.6% in the overall study population and was lower with canakinumab 150 mg SC q4wk than in the other three treatment group. AEs were mostly mild to moderate in intensity and did not appear to be related to either dose or age. SAEs or clinically significant AEs were reported in 4.7% of the overall study population, with a lower incidence in the canakinumab 150 mg SC q4wk group than in the other three groups. No deaths occurred. The number of discontinuations due to AEs was likewise lowest with canakinumab 150 mg SC q4wk. No severe reactions occurred.
Main results	Among 274 patients with evaluable efficacy data, the percentage of responders according to American College of Rheumatology 50 criteria (the primary endpoint, based on a 28-joint count) was significantly higher with canakinumab 150 mg SC q4wk than with placebo (26.5% vs 11.4%, respectively; p=0.028). Compared to placebo, this dosage of canakinumab was also associated with significantly more favorable responses at week 12 with respect to secondary endpoints including the Disease Activity Score 28, scores on the Health Assessment Questionnaire and Functional Assessment of Chronic Illness Therapy-Fatigue, swollen 28-joint count, and patient' s and physician' s global assessments of disease activity. No safety concerns were raised with canakinumab therapy, particularly regarding infections. Few injection-site reactions occurred.
Follow-up	12 weeks
Conclusions	The addition of canakinumab 150 mg SC q4wk improves therapeutic responses among patients who have active RA despite stable treatment with methotrexate.

Alten et al., 2015	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=350) ≈ Female 84% ≈ Age, years: MR prednisone: 57.1, Placebo: 57.5 ≈ Disease duration 8 years
Intervention(s)	Delayed-release (DR) prednisone 5 mg
Intervention(s) characteristics	Delayed-release (DR) prednisone is designed for evening administration (approximately 22:00) and releases 4 h later to coincide with the rise of nocturnal inflammatory cytokines associated with development of morning stiffness. Treatment with DR prednisone 5 mg or placebo once daily with or after the evening meal, in addition to existing stable DMARD treatment. Patients were randomised 2:1 to receive additional therapy with DR prednisone 5 mg or placebo once daily for 12 weeks.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	There was a statistically significant difference between treatments in the change from baseline to week 12 in FACIT-F score (LSM difference 2.2, p=0.0032), favouring DR prednisone, as compared with placebo. The within-group change from baseline to week 12 in FACIT-F score was clinically meaningful with DR prednisone/DMARD (3.8) but not with placebo/DMARD (1.6). Compared with placebo/DMARD, DR prednisone/DMARD showed significantly greater improvement in SF-36 vitality domain score (5.6, p=0.001). Furthermore, those who received DR prednisone and who reached ACR20 response had statistically better FACIT-F scores as compared with those not reaching ACR20 response (5.5 vs 2.2, p<0.0001). There was also correlation between FACIT-F score and response status defined by DAS28.
Safety results	Not stated
Main results	The change from baseline to week 12 in FACIT-F score was statistically significantly different with DR prednisone/DMARD (3.8) vs placebo/ DMARD (1.6; difference 2.2, p=0.0032). Improvement in FACIT-F score correlated positively with clinical response. Compared with placebo/DMARD, DR prednisone/DMARD showed a significantly greater improvement in SF-36 vitality score (5.6, p=0.001), physical component of SF-36 (2.3, p=0.0003) and general score with FACT-G (2.6, p=0.0233).
Follow-up	12 weeks
Conclusions	DR prednisone in addition to a DMARD significantly improves fatigue and other aspects of health-related quality of life in patients with symptomatic RA compared with DMARD treatment alone.

Bae et al., 2013	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=300) ≈ Female: ETN + MTX group: 91.4%, DMARD + MTX group: 88.4% ≈ Age, years: ETN + MTX group: 48.4, DMARD + MTX group: 48.5 ≈ Disease duration, years: ETN + MTX group: 6.5, DMARD + MTX group: 6.9 1987 ACR criteria
Intervention(s)	ETN + MTX
Intervention(s) characteristics	Patients were randomized to either of two treatment groups in an approximate 2:1 ratio: ETN + MTX (n=197) or to DMARD + MTX (n=103). ETN was administered subcutaneously (25 mg per injection) twice weekly. The dose and administration of usual DMARD therapy (defined as the addition of DMARD investigator's choice to MTX) followed the standard of care and approved local label or recommendations; the three most frequently used DMARDs in the study were leflunomide (n=69), sulfasalazine (n=23) and hydroxychloroquine (n=11). MTX was to be taken orally once weekly as a single dose or in two divided doses on the same day (per local label) and was continued at the same dose throughout the study as at the time of screening (n=300). Folic acid supplementation was recommended to all patients to minimize side effects associated with MTX.
Control	DMARD + MTX
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Both groups reported similar fatigue rating scores at baseline using the FACIT-F instrument, however the mean percentage improvement in the FACIT-Fatigue scale was significantly greater in the ETN + MTX group compared with the DMARD group at week 16 (28.0% vs 10.4%, p=0.001).
Safety results	No detailed information
Main results	Significantly greater improvements were noted for the ETN + MTX group at week16 for HAQ mean scores and for proportion of patients achieving HAQ score≤0.5, compared to patients in the DMARD + MTX group. SF-36 Summary Scores for physical and mental components and for 6 of 8 health domains showed significantly greater improvements at week16 for the ETN + MTX group; only scores for physical functioning and role-emotional domains did not differ significantly between the two treatment arms. Greater improvements at week 16 were noted for the ETN + MTX group for FACIT-F, HADS, and WPAI:GH mean scores.
Follow-up	16 weeks
Conclusions	Combination therapy using ETN + MTX demonstrated superior improvements using a comprehensive set of PRO measures, compared to combination therapy with usual standard of care DMARDs plus MTX in patients with established rheumatoid arthritis from the Asia-Pacific region.

Baranauskaite et al., 2012	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=115) ≈ Female: ETN + MTX group: 91.4%, DMARD + MTX group: 88.4% ≈ Age, years: ETN + MTX group: 48.4, DMARD + MTX group: 48.5 ≈ Disease duration, years: ETN + MTX group: 6.5, DMARD + MTX group: 6.9 Active PsA who were naive to methotrexate and not receiving disease-modifying therapy
Intervention(s)	Infliximab plus methotrexate
Intervention(s) characteristics	Infliximab (5 mg/kg) at weeks 0, 2, 6 and 14 plus methotrexate (15 mg/week). In both groups, methotrexate could be increased to 20 mg/week at week 6 if improvement of 20% in the American College of Rheumatology (ACR) response criteria (ACR20) was not achieved.
Control	Methotrexate (15 mg/week) alone
Outcomes of interest (types and measuring instruments)	Fatigue - VAS (visual analogue scale) Fatigue was a secondary outcome
Effectiveness results	The reduction from baseline in fatigue score was greater in the infliximab plus methotrexate group compared with the methotrexate-alone group at all-time points. At week 16, the mean reduction from baseline was 70.8% in the infliximab plus methotrexate group compared with 44.0% in the methotrexate-alone group (p=0.0003).
Safety results	The incidence of AE was higher in patients receiving infliximab plus methotrexate vs methotrexate alone. Most AE were mild or moderate. In the infliximab plus methotrexate group, 26 of 57 subjects (45.6%) had one or more treatment-related AE, and in the methotrexate-alone group, 13 of 54 subjects (24.1%) had one or more treatment-related AE. The most frequent treatment-related AE involved hepatic enzyme increases. Other AE leading to discontinuation in the infliximab plus methotrexate group included generalised oedema, pain, pyrexia, folliculitis, upper respiratory tract infection, dyspnoea and blood bilirubin increase (two patients). In the methotrexate-alone group, AE leading to discontinuation included diarrhoea, gastritis, nausea, vomiting and dizziness.
Main results	At week 16, 86.3% of patients receiving infliximab plus methotrexate and 66.7% of those receiving methotrexate alone achieved an ACR20 response (p<0.02). Of patients whose baseline PASI was 2.5 or greater, 97.1% receiving infliximab plus methotrexate compared with 54.3% receiving methotrexate alone experienced a 75% or greater improvement in PASI (p<0.0001). Improvements in C-reactive protein levels, DAS28 response and remission rates, dactylitis, fatigue and morning stiffness duration were also significantly greater in the group receiving infliximab. In the infliximab plus methotrexate group, 46% (26/57) had treatment related adverse events (AE) and two patients had serious AE, compared with 24% with AE (13/54) and no serious AE in the methotrexate-alone group.
Follow-up	16 weeks
Conclusions	Treatment with infliximab plus methotrexate in methotrexate-naive patients with active PsA demonstrated significantly greater ACR20 response rates and PASI75 improvement compared with methotrexate alone and was generally well tolerated.

Bingham et al., 2014	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=592) ≈ Female 81.6% ≈ Age 51.8 years ≈ Disease duration 6.9 years Active rheumatoid arthritis (RA) despite prior MTX therapy.
Intervention(s)	Intravenous (IV) golimumab 2 mg/kg
Intervention(s) characteristics	Adult patients with active RA despite MTX therapy were randomly assigned (2:1) to receive IV infusions of golimumab 2 mg/kg or placebo at weeks 0, 4, 12, and 20. All patients continued to receive a stable regimen of concomitant oral MTX (15–25 mg/wk). Randomization was stratified according to baseline C-reactive protein (CRP) level (< or ≥ 1.5 mg/dl; upper limit of normal: 1.0 mg/dl). At Week 16, patients in the placebo + MTX group who had less than 10% improvement in tender and swollen joint counts entered blinded early escape and crossed over to receive golimumab 2 mg/kg at weeks 16 and 20. Patients randomized to golimumab 2 mg/kg + MTX received placebo infusions at Week 16 to maintain the blind but did not undergo dose increase or changes in dosing frequency. Data collected through Week 24 are included in the current report.
Control	IV placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	Measurements of fatigue improved through Week 24 for patients who received golimumab + MTX. At weeks 12, 16, and 24, mean improvements in FACIT-F scores were significantly greater in the golimumab + MTX group than in the placebo + MTX group (In 24 weeks, FACIT-F scores were 2.54±10.22 and 7.96±10.79 in placebo+MTX and golimumab 2 mg/kg+MTX, respectively, p<0.001).
Safety results	Not stated
Main results	Mean HAQ-DI improvements from baseline were significantly greater with golimumab + MTX than placebo + MTX at Week 14 and Week 24 (p<0.001). Significantly greater improvements in all 8 individual SF-36 subscores and both the SF-36 PCS and MCS scores (p<0.001) also accompanied golimumab + MTX therapy. Improved EQ-5D and EQ-5D VAS (p<0.001) and FACIT-F (p<0.001) scores were also observed for golimumab + MTX-treated patients at Week 12, Week 16, and Week 24, and greater proportions of golimumab + MTX-treated patients had clinically meaningful improvements in these measures. Greater reductions in disease effect on productivity were observed with golimumab + MTX vs placebo + MTX at Week 24 (p<0.001). Improvements in physical function, HRQOL, fatigue, and productivity significantly correlated with disease activity improvement.
Follow-up	24 weeks
Conclusions	In active RA, IV golimumab + MTX significantly improved physical function, HRQOL, fatigue, and productivity using multiple measurement tools; all correlated with improvements in disease activity.

Bird et al., 2019	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=3061) ≈ Female (%): **In tofacitinib 5 mg two times a day (n=1194) group:** 85.25; **In tofacitinib 10 mg two times a day (n=1197) group**: 87; **In placebo group:** 83 ≈ Age, median (years): **In tofacitinib 5 mg two times a day (n=1194) group:** 53.25; **In tofacitinib 10 mg two times a day (n=1197) group**: 53.75; **In placebo group:** 51.75 ≈ Disease duration, years: **In tofacitinib 5 mg two times a day (n=1194) group:** 8.25; **In tofacitinib 10 mg two times a day (n=1197) group**: 8.82; **In placebo group:** 9.2
Intervention(s)	Tofacitinib 5 or 10 mg two times a day
Intervention(s) characteristics	Subgroup data were pooled across five Phase III randomised, placebo-controlled, double-blind studies of 6 to 24 months' duration. Tofacitinib was administered at 5 or 10 mg two times a day, either as monotherapy (ORAL Solo, ClinicalTrials.gov number: NCT00814307)29 or in combination with csDMARDs, mainly MTX (ORAL Sync: NCT00856544;30 ORAL Standard: NCT00853385;33 ORAL Scan: NCT0084761332 and ORAL Step: NCT0096044028) in patients with moderately to severely active RA and an inadequate response to ≥1 csDMARD or biologic DMARD. One Phase III study (ORAL Standard) included an active comparator of adalimumab (40 mg subcutaneously once every 2 weeks). Patients were permitted stable background doses of low-dose oral GCs and non-steroidal anti-inflammatory drugs. For this analysis, patients were categorised as: anti-CCP and RF positive (anti-CCP+/RF+); anti-CCP+/ RF negative (-); anti-CCP-/RF+; anti-CCP-/RF-. The following efficacy endpoints were evaluated at month 3 in patients receiving tofacitinib 5 or 10 mg two times a day or placebo for each serotype subgroup: proportions of patients achieving ACR20/50/70 response (defined as 20%, 50% or 70% improvement in ACR criteria, respectively) and Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4[ESR])-defined remission (<2.6) and LDA (≤3.2). Patient-reported outcomes (PROs) were also evaluated at month 3 and included changes from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI), Short Form-36 Health Survey (SF-36) physical functioning domain and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	Improvements from baseline in FACIT-F were significantly greater in patients receiving tofacitinib 5 or 10 mg two times a day compared with placebo across all serotype subgroups (all p≤0.05 vs placebo).
Safety results	Safety was assessed based on reporting of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), discontinuations due to AEs, serious infections, herpes zoster infections, malignancies (excluding non-melanoma skin cancer [NMSC]) and NMSC. Frequencies of AEs were similar across all treatment groups and serotype subgroups. Across serotype subgroups, TEAEs were observed in: 47.8%-54.3% of patients receiving tofacitinib 5 mg two times a day; 47.8%-57.4% of patients receiving tofacitinib 10 mg two times a day; and 50.2%-58.3% of patients receiving placebo. SAEs were observed in: 2.2%-3.5% of patients receiving tofacitinib 5 mg two times a day; 1.7%-4.4% of patients receiving tofacitinib 10 mg two times a day and 2.5%-5.7% of patients receiving placebo.
Main results	This post hoc analysis pooled data from 3061 patients. Of these, 1194 received tofacitinib 5 mg two times a day, 1197 received tofacitinib 10 mg two times a day and 670 received placebo. Baseline demographics/characteristics were similar across subgroups. Tofacitinib significantly improved ACR20/50/70 response rates, DAS28-4(ESR) LDA rates and CFB in HAQ-DI and FACIT-F vs placebo across subgroups. More anti-CCP+/RF+ than anti-CCP-/ RF- patients had ACR20/50/70 responses (ACR20/50: both tofacitinib doses; ACR70: 10 mg two times a day). SF-36 physical functioning improved in anti-CCP+/ RF+, anti-CCP+/RF- and anti-CCP-/RF+ patients (both tofacitinib doses) and anti-CCP-/RF- patients (10 mg two times a day) vs placebo. More anti-CCP+/RF+ and antiCCP+/RF- than anti-CCP-/RF- patients achieved DAS28- 4(ESR) remission and LDA with tofacitinib 10 mg two times a day. Frequency of adverse events (AEs), serious AEs and discontinuations due to AEs were similar across subgroups.
Follow-up	3 months
Conclusions	Generally, tofacitinib efficacy (ACR 20/50/70 responses) and safety were similar across subgroups. DAS28-4(ESR) remission rates and SF-36 physical functioning appeared lower in anti-CCP- patients.

Bowman et al., 2017	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren's syndrome (SS) patients (n=133) ≈ Female 93.2% ≈ Age 54.4 years ≈ Disease duration 5.7 years
Intervention(s)	IV rituximab (1,000 mg in 250 ml saline)
Intervention(s) characteristics	Rituximab is a monoclonal antibody against CD20 (a cell surface antigen expressed on B cells). Treatment with rituximab induces a rapid and sustained depletion of B cells. Patients were ages 18–80 years, were positive for anti-Ro autoantibodies, and had some (greater than zero) unstimulated salivary flow, symptomatic fatigue, and oral dryness worse than 5 of 10 on a self-completed Likert scale. Eligible participants had to be receiving a stable dose of corticosteroids, nonsteroidal anti-inflammatory drugs, DMARDs, pilocarpine, and antidepressants for 4 weeks prior to and throughout the study, and they had to provide written informed consent to participate. Rituximab was provided free of charge to the study by Hoffmann-La Roche. Participants received either intravenous (IV) rituximab (1,000 mg in 250 ml saline) or IV placebo (250 ml saline) in 2 courses at weeks 0, 2, 24, and 26. To reduce risk of infusion reactions, patients received methylprednisolone, acetaminophen, and chlorpheniramine pre-infusion and oral prednisolone post-infusion, tapering from 60 mg/day to 15 mg/day over 7 days post-infusion.
Control	IV placebo (250 ml saline)
Outcomes of interest (types and measuring instruments)	Fatigue - (VAS-Fatigue) Fatigue was a primary outcome
Effectiveness results	The primary end point response rates among patients with complete data were 37.5% for placebo-treated patients (21 of 56) and 39.3% for rituximab-treated patients (24 of 61). After multiple imputation of missing responses, the mean response rates were 36.8% and 39.8% for the placebo and rituximab treatment arms, respectively (unadjusted absolute difference 3.0%, 95% CI=214.5 to 20.5). In the primary analysis, rituximab-treated patients were not significantly more likely than placebo-treated patients to achieve 30% reduction in fatigue or oral dryness (OR=1.13, 95% CI=0.50 to 2.55, p=0.76). The baseline-adjusted absolute difference in response rates (rituximab-placebo) was 1.7% (95% CI=216.5 to 19.1, p=0.84). The lack of significant treatment effect remained even when using different end point imputation strategies or a complete-case analysis. A per-protocol population analysis (excluding patients found to be ineligible, those not receiving all 4 doses within a reasonable time frame, and those with incomplete primary end point data) also did not yield significant results (OR=0.9, 95% CI=0.1 to 6.5, p=0.95). Longitudinal analyses of patient VAS values did not reveal significant differences in change over time between randomized treatment arms for fatigue-VAS scores. There were no significant differences between the groups at any time point for this or any of the other symptom scales.
Safety results	Rituximab was well-tolerated among patients. There were no deaths in either treatment arm. There were 10 serious AEs (SAEs) among 9 patients in each treatment arm, of which 3 events in 3 patients in each treatment arm were serious adverse reactions. One participant randomized to receive rituximab did not receive any rituximab prior to having an SAE. One serious infusion reaction was reported in 1 patient receiving rituximab, and 1 serious anaphylaxis event was reported in 1 patient receiving placebo. For nonserious AEs, 275 were reported in 55 placebo-treated patients, of which 61 (22.2%) were suspected to be related to treatment, 24 (8.7%) resulted in delayed or modified treatment administration, and 5 (1.8%) resulted in cessation of treatment; 325 nonserious AEs were reported in 61 rituximab treated patients, of which 82 (25.2%) were suspected to be related to treatment, 33 (10.2%) resulted in delayed or modified treatment administration, and 10 (3.1%) resulted in cessation of treatment.
Main results	All 133 patients who were randomized to receive placebo (n=66) or rituximab (n=67) were included in the primary analysis. Among patients with complete data, 21 of 56 placebo-treated patients and 24 of 61 rituximab-treated patients achieved the primary end point. After multiple imputation of missing outcomes, response rates in the placebo and rituximab groups were 36.8% and 39.8%, respectively (adjusted OR=1.13, 95% CI=0.50 to 2.55). There were no significant improvements in any outcome measure except for unstimulated salivary flow. The mean 6 SD costs per patient for rituximab and placebo were £10,752±264.75 and £2,672±241.71, respectively. There were slightly more adverse events (AEs) reported in total for rituximab, but there was no difference in serious AEs (10 in each group).
Follow-up	48 weeks
Conclusions	The results of this study indicate that rituximab is neither clinically effective nor cost effective in this patient population.

Braun et al., 2007	
Participants characteristics (number, age, disease criteria, details)	AS patients (n=356) ≈ Female, %: Etanercept 50 mg QW: 30, Etanercept 25 mg BIW: 24, Placebo group: 22 ≈ Age, years: Etanercept 50 mg QW: 41, Etanercept 25 mg BIW: 40, Placebo group: 40 ≈ Disease duration, years: Etanercept 50 mg QW: 9, Etanercept 25 mg BIW: 10, Placebo group: 8 AS according to the Modified New York Criteria
Intervention(s)	Etanercept 50 mg once-weekly (QW), etanercept 25 mg twice-weekly (BIW)
Intervention(s) characteristics	This study compared etanercept 50 mg QW, etanercept 25 mg BIW and placebo (3:3:1 ratio).
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue – Bath Ankylosing Spondylitis Activity Index (BASDAI)-fatigue item Fatigue was a primary outcome
Effectiveness results	For BASDAI-fatigue, by week 8, mean improvement from baseline for both etanercept groups was significantly higher than that for the placebo group. Improvement was comparable with no significant differences between etanercept 50 mg QW and etanercept 25 mg BIW). Significant difference between etanercept 50 mg QW and placebo at weeks 4, 8 and 12: $p<0.05$, $p<0.01$ and $p<0.0001$, respectively. Significant difference between etanercept 25 mg BIW and placebo at weeks 8 and 12: $p<0.05$ and $p<0.01$, respectively.
Safety results	Incidence of treatment-emergent adverse events, including infections, was similar among all three groups, and no unexpected safety issues were identified.
Main results	Consistent with earlier reports, AS was associated with quality of life (QOL) impairment and functional limitations, similar to or worse than cancer, congestive heart failure, diabetes or depression. Treatment with etanercept 50 mg QW or 25 mg BIW significantly improved QOL and functional status compared with placebo. High proportions of patients achieved clinically meaningful improvements in all PRO measures, including physical function, fatigue, pain, psychosocial domains, and general health status. Improvements were similar with the two etanercept dose regimens.
Follow-up	12 weeks
Conclusions	The more convenient etanercept 50 mg QW dose regimen significantly improves function and QOL in patients with AS, similarly to the standard dosing of 25 mg BIW, supporting its use for AS therapy.

Braun et al., 2009	
Participants characteristics (number, age, disease criteria, details)	AS patients (n=256) ≈ Female, %: Infliximab group: 10, Placebo group: 21 ≈ Age, years: Infliximab group: 40, Placebo group: 39.3 ≈ Disease duration, years: Infliximab group: 11.5, Placebo group: 10.3
Intervention(s)	Infliximab 5 mg/kg
Intervention(s) characteristics	Patients with AS were randomly assigned to receive placebo or infliximab 5 mg/kg at weeks 0, 2, 6, 12, and 18.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue – Visual analog scale (VAS) Fatigue was a primary outcome
Effectiveness results	Patients treated with infliximab demonstrated statistically significant improvements in mean fatigue VAS score (-2.4 vs -0.4; p<0.001) at week 24 when compared with patients in the placebo group.
Safety results	Not stated
Main results	At baseline, 11 placebo group patients (16.2%) and 37 infliximab group patients (19.7%) had anemia. Of these, more infliximab-treated patients achieved normal hemoglobin levels at week 24 compared with patients receiving placebo (70.3% vs 27.3%; p=0.01). Infliximab-treated patients had significant improvements in mean hemoglobin concentration (0.7 gm/dl vs 0.3 gm/dl), BASFI score (2.1 vs 0.2), and fatigue VAS score (2.4 vs 0.4) compared with placebo patients (p<0.001). Multiple regression analyses showed that improvements in hemoglobin level were significantly and independently associated with improvements in physical function and fatigue. Infliximab-treated patients with elevated CRP or IL-6 levels at baseline were more likely than those with low levels to have improvement in hemoglobin levels.
Follow-up	18 weeks
Conclusions	Infliximab treatment significantly decreased the proportion of AS patients with anemia and improved hemoglobin levels compared with placebo. Improvement in hemoglobin level was independently associated with improvements in physical function and fatigue.

Burmester et al., 2013	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=399) ≈ Female 84% ≈ Age, years: Tofacitinib 5 mg group: 55.4, Tofacitinib 10 mg group: 55.1, Placebo group: 54.4 ≈ Disease duration, years: Tofacitinib 5 mg group: 13, Tofacitinib 10 mg group: 12.6, Placebo group: 11.3
Intervention(s)	Tofacitinib 5 or 10 mg
Intervention(s) characteristics	Patients were randomly assigned in a 2:2:1:1 ratio to tofacitinib 5 mg twice a day; tofacitinib 10 mg twice a day; placebo for 3 months then advanced to 5 mg tofacitinib twice a day; or placebo for 3 months then advanced to 10 mg tofacitinib twice a day, all with stably dosed methotrexate. For analyses of tofacitinib versus placebo for months 0–3, data from the two placebo sequences were combined into one group.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Improvements in FACIT-F at month 3 were 6.3 (n=117; [2.77–7.54]; p<0.0001) for tofacitinib 5 mg twice a day and 4.6 (n=125; [1.09–5.83]; p=0.0043) for tofacitinib 10 mg twice a day versus 1.1 (n=114) for placebo.
Safety results	Differences in mean changes from baseline in laboratory parameters noted for tofacitinib 5 and 10 mg twice a day versus placebo included decreases in neutrophil counts and increases in cholesterol (HDL and LDL) concen trations (table 3, appendix). No patient had a confi rmed potential life-threatening absolute neutrophil count of less than 0.5×10⁹/L (table 3). All mean laboratory safety values stabilised after month 3. The safety profi le of tofacitinib was consistent with previous phase 2 and phase 3 studies.
Main results	At month 3, ACR20 response rates were 41.7% (55 of 132 [95% CI vs placebo 6.06–28.41]; p=0.0024) for tofacitinib 5 mg twice a day and 48.1% (64 of 133; [12.45–34.92]; p<0.0001) for tofacitinib 10 mg twice a day versus 24.4% (32 of 131) for placebo. Improvements from baseline in HAQ-DI were −0.43 ([−0.36 to −0.15]; p<0.0001) for 5 mg twice a day and −0.46 ([−0.38 to −0.17]; p<0·0001) for 10 mg twice a day tofacitinib versus −0.18 for placebo; DAS28<2.6 rates were 6.7% (eight of 119; [0–10.10]; p=0.0496) for 5 mg twice a day tofacitinib and 8.8% (11 of 125 [1.66–12.60]; p=0.0105) for 10 mg twice a day tofacitinib versus 1.7% (two of 120) for placebo. Safety was consistent with phase 2 and 3 studies. The most common adverse events in months 0–3 were diarrhoea (13 of 267; 4.9%), nasopharyngitis (11 of 267; 4.1%), headache (11 of 267; 4.1%), and urinary tract infection (eight of 267; 3.0%) across tofacitinib groups, and nausea (nine of 132; 6.8%) in the placebo group.
Follow-up	6 months
Conclusions	In this treatment-refractory population, tofacitinib with methotrexate had rapid and clinically meaningful improvements in signs and symptoms of rheumatoid arthritis and physical function over 6 months with manageable safety. Tofacitinib could provide an eff ective treatment option in patients with an inadequate response to TNFi.

Calin et al., 2004	
Participants characteristics (number, age, disease criteria, details)	AS patients (n=84) ≈ Female 21% ≈ Age 43.2 years ≈ Disease duration 12.5 years Diagnosed using the modified New York criteria
Intervention(s)	Etanercept (25 mg twice weekly)
Intervention(s) characteristics	Patients were randomly assigned to 25 mg injections of etanercept or placebo twice weekly for 12 weeks. The study included a screening period of up to 4 weeks, followed by a 12-week treatment period in which patients received etanercept or placebo. Efficacy and safety evaluations were performed at weeks 2, 4, 8, and 12. A 25 mg dose delivered subcutaneously twice weekly was selected for patients with AS.
Control	Placebo
Outcomes of interest (types and measuring instruments)	BASDAI - Fatigue Fatigue was a secondary outcome
Effectiveness results	Scores on the BASDAI composite index and the BASDAI fatigue component improved 44% among etanercept patients ($p<0.01$ vs placebo). % change of BASDAI-fatigue at 12 weeks was 43.6 and 13.6 in etanercept and placebo groups, respectively. % change of BASDAI-fatigue at 12 weeks was 42.6 and -4.9 in etanercept and placebo groups, respectively.
Safety results	Patients were monitored for adverse events and abnormal laboratory test results over the course of the study. Vital signs were monitored, and standard haematology, serum chemistry, and urine analysis tests were evaluated. In addition, blood samples were tested for antibody to etanercept at baseline and at week 12, using an enzyme linked immunosorbent assay (ELISA) modified from the method published earlier. Etanercept was well tolerated. Most adverse events were mild to moderate; the only between-group difference was injection site reactions, which occurred significantly more often in etanercept patients.
Main results	Of 84 patients enrolled, 45 received etanercept and 39 received placebo. Significantly more etanercept patients than placebo patients responded at the ASAS 20 level as early as week 2, and sustained differences were evident up to week 12. Significantly more etanercept patients reported ASAS 50 responses at all times and ASAS 70 responses at weeks 2, 4, and 8; reported lower composite and fatigue BASDAI scores; had lower acute phase reactant levels; and had improved spinal flexion.
Follow-up	12 weeks
Conclusions	Etanercept is a well-tolerated and effective treatment for reducing clinical symptoms and signs of AS.

Chung et al., 2007	
Participants characteristics (number, age, disease criteria, details)	Idiopathic Inflammatory Myopathies (IIM) patients (n=37) ≈ Female 84% ≈ Age, years: Creatine group: 59, Placebo group: 50 ≈ Disease duration, years: Creatine group: 9.2, Placebo group: 8.6
Intervention(s)	Oral creatine supplements (8 days, 20 gm/day then 3 gm/day)
Intervention(s) characteristics	In a 6-month, 2-center, double-blind, randomized controlled trial, patients were randomized to receive oral creatine supplements (8 days, 20 gm/day then 3 gm/day) or placebo. All patients followed a home exercise program. The primary outcome was aggregate functional performance time (AFPT), reflecting the ability to undertake high-intensity exercise. Patients were receiving stable immunosuppressive treatment and/or corticosteroids.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Chalder fatigue score Fatigue was a secondary outcome
Effectiveness results	Chalder fatigue scores did not change with treatment and showed no differences between groups.
Safety results	There were 22 adverse events in 13 patients (6-7 in each group), including 8 infections, 6 falls, and 2 gastrointestinal events (gastric ulcer and bowel symptoms requiring colonoscopy). None of the reactions was considered as being related to creatine treatment or other medication administered to treat IIM during the trial.
Main results	A total of 37 patients with polymyositis or dermatomyositis were randomized (19 to creatine, 18 to placebo); 29 completed 6 months. Intent-to-treat analyses demonstrated that AFPT improved significantly at 6 months with creatine (median decrease 13%, range=32 to 8%) compared with placebo (median decrease 3%, range=13 to 16%; p=0.029). A completer analysis also showed significant benefits from creatine (p=0.014). The functional index improved significantly with both creatine and placebo ($p<0.05$), with a significant benefit between groups in the completer analysis only. Phosphocreatine/-nucleoside triphosphate ratios using MRS increased significantly in the creatine group ($p<0.05$) but not in the control group. No clinically relevant adverse events were associated with creatine.
Follow-up	6 months
Conclusions	Oral creatine supplements combined with home exercises improve functional performance without significant adverse effects in patients with polymyositis or dermatomyositis. They appear safe, effective, and inexpensive.

Cohen et al., 2006	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=517) ≈ Female 81% ≈ Age, years: Rituximab group: 52.8, Placebo group: 52.2 ≈ Disease duration, years: Rituximab group: 11.7, Placebo group: 12.1 RA according to the ACR 1987 revised criteria
Intervention(s)	Rituximab
Intervention(s) characteristics	Patients with active RA and an inadequate response to 1 or more anti-TNF agents were randomized to receive intravenous rituximab (1 course, consisting of 2 infusions of 1,000 mg each) or placebo, both with background MTX.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Patients receiving rituximab reported a significant reduction in fatigue, as measured by the FACIT-F scale, which decreased by a mean of 9.1 points, representing a 29.6% improvement from baseline ($p<0.0001$); patients receiving placebo reported a mean decrease of 0.5 points in the FACIT-F score.
Safety results	Overall, 88% of placebo-treated patients reported an adverse event during the study period, as compared with 85% of rituximab-treated patients. Most AEs were mild or moderate in severity (CTC grade 1 or 2), with 23% of patients in the placebo group and 18% in the rituximab group experiencing severe adverse events (CTC grade 3 or 4). Serious AEs were reported in more patients receiving placebo (10%) than in those receiving rituximab (7%). Two patients in the placebo group withdrew from the study because of AEs (1 because of gastric cancer and 1 because of thrombocytosis). Eight patients in the rituximab group withdrew because of AEs, 5 because of infusion-related reactions during the first infusion (anaphylactic reaction, urticaria, laryngeal edema, and cough and hoarseness) and 3 because of other events (cardiac tamponade, spontaneous abortion, and progressive RA). There were no deaths recorded during the 24-week double-blind portion of the study.
Main results	Patients assigned to placebo (n=209) and rituximab (n=311) had active, longstanding RA. At week 24, significantly more ($p<0.0001$) rituximab treated patients than placebo-treated patients demonstrated ACR20 (51% vs 18%), ACR50 (27% vs 5%), and ACR70 (12% vs 1%) responses and moderate-to-good EULAR responses (65% vs 22%). All ACR response parameters were significantly improved in rituximab-treated patients, who also had clinically meaningful improvements in fatigue, disability, and health-related quality of life (demonstrated by FACIT-F, HAQ DI, and SF-36 scores, respectively) and showed a trend toward less progression in radiographic end points. Rituximab depleted peripheral CD20 B cells, but the mean immunoglobulin levels (IgG, IgM, and IgA) remained within normal ranges. Most adverse events occurred with the first rituximab infusion and were of mild-to-moderate severity. The rate of serious infections was 5.2 per 100 patient-years in the rituximab group and 3.7 per 100 patient-years in the placebo group.
Follow-up	24 weeks
Conclusions	At 24 weeks, a single course of rituximab with concomitant MTX therapy provided significant and clinically meaningful improvements in disease activity in patients with active, longstanding RA who had an inadequate response to 1 or more anti-TNF therapies.

Dass et al., 2008	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren syndrome (pSS) patients (n=17) ≈ Female 81% ≈ Age, years: Rituximab group: 51, Placebo group: 54 ≈ Disease duration, years (median): Rituximab group: 7.3, Placebo group: 8.3 Fulfilled the American–European Consensus Criteria for pSS
Intervention(s)	Rituximab 1 g
Intervention(s) characteristics	A total of 17 patients with pSS and a score on fatigue visual analogue scale (VAS) > 50 were randomised to receive either 2 infusions of rituximab 1 g or placebo; patients also received oral and intravenous steroids.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy– Fatigue (FACIT-F), VAS-fatigue Fatigue was a primary outcome
Effectiveness results	At 6 months, seven of eight patients receiving rituximab (87.5%) and five of nine patients receiving placebo (55.6%) demonstrated >20% improvement in fatigue VAS (p=0.36). The mean improvement in fatigue VAS at 6 months was 49.5% (rituximab) vs 20.5% (placebo) (p=0.24). Using 30% improvement from baseline as a threshold for defining response, the number of rituximab responders was unchanged but fewer placebo patients (four of nine) achieved response (p=0.06). There was significant improvement from baseline in fatigue VAS in the rituximab group (mean±SD improvement=36.8±17.9, p<0.001) in contrast to the placebo group (17.3±32.2, p = 0.15). Change in fatigue over time between the two groups indicated that the rituximab treated patients had greater reduction in fatigue than the placebo group at each month between treatment and 6 months afterwards. The change in fatigue VAS was much more variable in the placebo group. In the placebo group, the change varied between approximately 99% improvement and 110% worsening (interquartile range 78%). In the active group the change varied between 83% improvement and 11% worsening (interquartile range 39%).
Safety results	Three serious adverse events (SAEs) occurred in two patients in the rituximab group. One patient developed symptoms of headache, urticarial rash, fever and meningism 7 days after the first infusion of rituximab. This was the second patient treated in the study and so she did not receive oral steroids as per the initial protocol. Infective meningitis was excluded, and a diagnosis of serum sickness was made. The patient responded well to intravenous steroids. Two patients in the rituximab group also experienced infusion reactions; these were both during the first infusion and consisted of rigors and a macular rash. The infusions were restarted and completed uneventfully after administration of antihistamine and hydrocortisone.
Main results	There was significant improvement from baseline in fatigue VAS in the rituximab group (p<0.001) in contrast to the placebo group (p=0.15). There was a significant difference between the groups at 6 months in the social functioning score of SF-36 (p=0.01) and a trend to significant difference in the mental health domain score of SF-36 (p=0.06). There was one episode of serum sickness in the rituximab treated group.
Follow-up	6 months
Conclusions	Rituximab in pSS shows benefit; further studies are justified.

Deodhar, et al. 2016	
Participants characteristics (number, age, disease criteria, details)	AS patients (n=371) ≈ Female 33% ≈ Age, years: Secukinumab IV→150 mg group: 40.1, Secukinumab IV→150 mg group: 42.3, Placebo group: 43.1 ≈ Disease duration, years: Secukinumab IV→150 mg group: 6.5, Secukinumab IV→150 mg group: 7.9, Placebo group: 8.3 Fulfilling the modified New York criteria
Intervention(s)	Secukinumab (interleukin-17A inhibitor)
Intervention(s) characteristics	371 patients received (1:1:1) intravenous secukinumab 10 mg/kg (baseline, weeks 2 and 4) followed by subcutaneous secukinumab 150 mg (IV→150 mg) or 75 mg (IV→75 mg) every 4 weeks or placebo.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	At week 16, improvement in mean changes from baseline for FACIT-F was greater in both secukinumab regimens compared with placebo.
Safety results	Not stated
Main results	At week 16, secukinumab IV→150 mg or IV→75 mg was associated with statistically and clinically significant improvements from baseline vs placebo in BASDAI (−2.3 for both regimens vs 0.6; p<0.0001 and p<0.001, respectively), SF-36 PCS (5.6 for both regimens vs 1.0; p<0.0001 and p<0.001, respectively), and ASQoL (−3.6, for both regimens vs −1.0; p<0.0001 and p<0.001, respectively). Clinically significant improvements in SF-36 MCS, BASFI, EQ-5D, and BASDAI 50 were observed with both secukinumab groups vs placebo at week 16; improvements were also observed in FACIT-F and WPAI-GH. All improvements were sustained through week 52.
Follow-up	52 weeks
Conclusions	Secukinumab provided significant and sustained improvements in patient-reported disease activity, health-related quality of life, and reduced functional impairment, fatigue, and impact of disease on work productivity in patients with active AS.

Deodhar et al., 2019	
Participants characteristics (number, age, disease criteria, details)	AS patients (n=146) ≈ Female, %: Secukinumab 150 mg group: 36, Placebo group: 24 ≈ Age, years: Secukinumab 150 mg group: 41.9, Placebo group: 43.6 ≈ Disease duration: not stated Fulfilling the modified New York criteria
Intervention(s)	Secukinumab 150 mg
Intervention(s) characteristics	Patients with active AS were randomised to receive secukinumab 150 mg, 75 mg, or placebo weekly until Week 4, and every 4 weeks thereafter.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	The mean improvement in FACIT-F total score from baseline was higher in the secukinumab 150 mg group compared to the placebo group at Week 4, which continued to improve through Week 104. Fatigue scores also improved in patients stratified by baseline hsCRP levels and prior TNFi therapy status. Improvement was seen with secukinumab at the earliest assessed time point of Week 4 in both hsCRP and TNFi subgroups. The mean change from baseline at Week 16 (secukinumab vs. placebo) was 7.1 vs 3.3 for normal hsCRP (p=0.15), 8.7 vs 3.6 (p<0.05) for elevated hsCRP, 10.0 vs 5.2 (p<0.05) for TNFinaïve and 5.7 vs 0.5 (p=0.06) for TNFi-IR groups. At Week 104, higher magnitudes of improvements in FACIT-Fatigue scores were observed in patients with elevated hsCRP (12.9) than normal hsCRP (8.3); however, improvements were comparable between TNFi-naïve (11.0) and TNFiIR (11.6) patients. Improvements in fatigue measured by BASDAI Question no. 1 were also observed in patients treated with secukinumab vs placebo at Week 16 across all groups (overall population, by baseline hsCRP levels, and by TNF status), which were sustained or further improved through Week 104.
Safety results	Not stated
Main results	Secukinumab-treated patients reported rapid improvement in pain and fatigue scores in overall population by Weeks 1 and 4, respectively; this trend of improvement was also observed irrespective of baseline hsCRP levels or prior TNFi therapy. Mean change at Week 16 in spinal/nocturnal pain (secukinumab vs. placebo) for the subgroups were -34.6/-30.2 vs -16.6/-10.0, p<0.05/0.01 (normal hsCRP); -26.7/-31.6 vs -7.8/-9.3, p<0.001/0.0001 (elevated hsCRP); -33.2/-35.4 vs -13.2/-14.9, both p<0.0001 (TNFi-naïve); and -22.5/-22.8 vs -9.4/-4.0, p=0.06/p<0.01 (TNFi-IR). FACIT-Fatigue was 7.1 vs 3.3, p=0.15 (normal hsCRP); 8.7 vs 3.6, p<0.05 (elevated hsCRP); 10.0 vs 5.2, p<0.05 (TNFi-naïve); and 5.7 vs 0.5, p=0.06 (TNFi-IR). These improvements were sustained or further improved through Week 104.
Follow-up	2 years
Conclusions	Secukinumab provides rapid and sustained relief of pain and fatigue over 2 years in patients with AS regardless of baseline hsCRP levels and prior TNFi therapy.

Deodhar et al., 2021	
Participants characteristics (number, age, disease criteria, details)	Non-radiographic axial spondyloarthritis (nr-axSpA) patients (n=303) ≈ Female, %: IXE Q4W group: 58, IXE Q2W group: 48, Placebo group: 52 ≈ Age, years: IXE Q4W group: 41, IXE Q2W group: 40, Placebo group: 40 ≈ Disease duration, years: IXE Q4W group: 4.2, IXE Q2W group: 3.4, Placebo group: 3.1
Intervention(s)	Ixekizumab
Intervention(s) characteristics	Ixekizumab is an interleukin-17A antibody. This study assessed the efficacy and safety of 80-mg ixekizumab every 2 weeks (Q2W) and every 4 weeks (Q4W) in patients with active nr-axSpA. Eligible patients were adults with an established diagnosis of axSpA by a physician and fulfilled the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA, with at least 12 weeks of previous therapy with NSAIDs and an inadequate response, as determined by the investigator, to two or more NSAIDs at the therapeutic dose range for a total duration of at least 4 weeks. 303 patients randomized 1:1:1 to receive placebo Q2W (n=105), 80-mg of ixekizumab Q4W (n=96), or 80mg of ixekizumab Q2W (n=102), via subcutaneous injection.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue Severity NRS, BASDAI-fatigue item Fatigue was a secondary outcome
Effectiveness results	At week 16, a significant improvement in Fatigue NRS was reported by patients receiving ixekizumab Q4W compared to placebo (p=0.02). Improvements in fatigue were not statistically significant with either ixekizumab dosing regimen at other time points. Similarly, improvements in BASDAI fatigue were numerically greater but not statistically significant with both ixekizumab dosing regimens at weeks 16 and 52.
Safety results	Not stated
Main results	Patients treated with ixekizumab Q2W and Q4W reported significantly greater improvements in PtGA, spinal pain, function, and stiffness at week 1, when these measures were first assessed, compared with placebo (p<0.05). ASAS40 responders, in comparison to ASAS20 non-responders, had the highest correlations with improvements in all response domains (PtGA, spinal pain, function, and stiffness) as well as fatigue and spinal pain at night (p<0.001). ASAS40 responses were associated with 3.5-to-48.0-fold greater improvements in these PROs, with the highest values for PtGA and function, compared to ASAS20 nonachievement.
Follow-up	52 weeks
Conclusions	As early as week 1, patients with nr-axSpA treated with ixekizumab reported significant improvements in PtGA, spinal pain, function, and stiffness compared with those taking placebo. ASAS40 responders reported significantly greater improvements in all ASAS response domains (PtGA, spinal pain, function, and stiffness) as well as fatigue and spinal pain at night than ASAS20 non-responders. Improvements in PtGA and function appear to be major drivers in achieving ASAS40 response in patients with nr-axSpA.

Devauchelle-Pensec et al., 2014	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren syndrome (pSS) patients (n=120) ≈ Female %: Rituximab group: 90.5, Placebo group: 96.5 ≈ Age, years: Rituximab group: 52.9, Placebo group: 55.6 ≈ Disease duration, years: Rituximab group: 4.6, Placebo group: 5.5 Fulfilled the American–European Consensus Group criteria for pSS
Intervention(s)	Rituximab
Intervention(s) characteristics	120 patients with scores of 50 mm or greater on at least 2 of 4 visual analogue scales (VASs) (global disease, pain, fatigue, and dryness) and recent-onset (10 years) biologically active or systemic pSS. Randomization (1:1 ratio) to rituximab (1 g at weeks 0 and 2) or placebo.
Control	Placebo
Outcomes of interest (types and measuring instruments)	VAS-fatigue score Fatigue was a secondary outcome
Effectiveness results	A 30-mm decrease in the VAS fatigue score was more common with rituximab than placebo at week 6 (absolute difference, 26.6 percentage points [95% CI=15.7 to 37.5 percentage points]; p=0.001) and week 16 (absolute difference, 18.3 percentage points [95% CI=4.1 to 32.6 percentage points]; p=0.012). The mean decrease in the VAS fatigue score was larger with rituximab than placebo at weeks 6, 16, and 24.
Safety results	Infusion reactions were significantly more common in the rituximab group. The only other significant between-group difference occurred for the proportion of patients who had at least 1 respiratory disorder (p=0.014) within 24 hours after an infusion. Rates of infection and severe infection were similar between groups (bronchitis and urinary and cutaneous infections were the more frequent manifestations in both groups), and no patients had opportunistic infections. In 2 patients receiving rituximab, cancer was diagnosed during routine investigations at 7 days (squamous cell carcinoma of the skin) and 38 days (breast cancer in a woman who died 1 year after inclusion) after enrollment. In 1 patient receiving placebo, superficial basal cell carcinoma was diagnosed 125 days after inclusion.
Main results	No significant difference between groups in the primary end point was found (difference, 1.0% [95% CI=16.7% to 18.7%). The proportion of patients with at least 30-mm decreases in at least two of the four VAS scores was higher in the rituximab group at week 6 (22.4% vs 9.1%; p=0.036). An improvement of at least 30 mm in VAS fatigue score was more common with rituximab at weeks 6 (p=0.001) and 16 (p=0.012), and improvement in fatigue from baseline to week 24 was greater with rituximab. Adverse events were similar between groups except for a higher rate of infusion reactions with rituximab.
Follow-up	24 weeks
Conclusions	Rituximab did not alleviate symptoms or disease activity in patients with pSS at week 24, although it alleviated some symptoms at earlier time points.

Dörner et al., 2019	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren syndrome (pSS) patients (n=27) ≈ Female %: Ianalumab 10 mg/kg group: 78, Ianalumab 3 mg/kg group: 83, Placebo group: 92 ≈ Age, years (median): Ianalumab 10 mg/kg group: 50, Ianalumab 3 mg/kg group:49, Placebo group: 58.5 ≈ Disease duration, years: not stated Fulfilling revised European US consensus criteria for pSS
Intervention(s)	Ianalumab (VAY736
Intervention(s) characteristics	Ianalumab (VAY736) is a B cell-depleting, B cell activating factor receptor-blocking, monoclonal antibody. Patients with pSS, EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) ≥6, were randomised to ianalumab single infusion at either 3 mg/kg (n=6), 10 mg/kg (n=12) or placebo (n=9). Patients meeting eligibility criteria were enrolled into two sequential cohorts. Ianalumab (150 mg lyophilisate) was reconstituted with water and diluted in 5% dextrose infusion bag. Placebo was administered as vehicle only. Paracetamol 500 mg was administered 1 hour prior and 5 hours after ianalumab dosing.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue-Multidimensional Fatigue Inventory (MFI) Fatigue was a secondary outcome
Effectiveness results	Early but transient response to treatment with 3 mg/kg ianalumab was observed at week 6 in all the MFI domains (statistically significant for general fatigue and physical fatigue), with scores returning to baseline by week 24. For the 3 mg/kg ianalumab group at week 6 there was a 5.4-point greater reduction from baseline in general fatigue score (95% CI=0.97 to 9.72) and in physical fatigue score there was a 4.4-point greater reduction from baseline (95% CI=0.87 to 7.96), both with statistical significance. In contrast, in the 10 mg/kg ianalumab group, early reductions were observed at week 6 for all MFI domains, sustained between week 6 and week 24, and continued to EoS for the MFI domains of general fatigue, physical fatigue and reduced activity.
Safety results	Most AEs were mild to moderate in severity without any severe AEs suspected related to ianalumab. The most observed AE was mild to moderate infusion-related reaction, characterised by acute onset within hours after ianalumab exposure of one or more of the following: headache, fever, chills, nausea and arthralgias. Fifteen patients receiving ianalumab experienced an infusion reaction (83.3%) compared with one placebo-treated patient (11.1%). Infusion reactions were mild (n=3) to moderate (n=12) in severity and not related to dose but did trend with the number of circulating B cells present at baseline; patients with moderate infusion-related reactions tend to have relatively higher B cell counts at baseline than those with mild reaction or none. All infusion-related reactions resolved within 24 hours either spontaneously or with additional paracetamol treatment. The reported incidence of nasopharyngitis was also higher in ianalumab-treated patients (n=6; 33.3%) vs placebo-treated patients (n=1; 11.1%). There was no increase in infections otherwise in the ianalumab group vs placebo group, nor in the incidence of other AEs over the 24-week, blinded study period.
Main results	A similar trend showing positive therapeutic effect by ianalumab was observed across the primary clinical outcome (ESSDAI) and all secondary clinical outcomes (ESSPRI, Multidimensional Fatigue Inventory, Short Form-36, global assessments by physician and patient) vs the placebo-treated group. Rapid and profound B cell depletion of long-lasting duration occurred after a single infusion of ianalumab at either dose. Serum Ig light chains decreased, with return to baseline levels at EoS. Changes in some clinical outcomes persisted through to EoS in the higher dose group. Adverse effects were largely limited to mild to moderate infusion reactions within 24 hours of ianalumab administration.
Follow-up	24 weeks
Conclusions	Overall results in this single-dose study suggest potent and sustained B cell depletion by ianalumab could provide therapeutic benefits in patients with pSS without major side effects.

Dougados et al., 2015	
Participants characteristics (number, age, disease criteria, details)	Nonradiographic axial spondyloarthritis (nr-axSpA) patients (n=215) ≈ Female 39.5% ≈ Age 32 years ≈ Disease duration 2.4 years Fulfilling the Assessment of Spondyloarthritis International Society axSpA criteria, not meeting the modified New York criteria for AS
Intervention(s)	Etanercept (ETN)
Intervention(s) characteristics	Enrolled patients were randomized (1:1) to receive either ETN 50 mg once weekly (QW) subcutaneously or PBO double-blind for 12 weeks. Patients in both treatment groups continued their background NSAID therapy at stable, optimal, tolerated dosages as determined by the study investigator.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue-Multidimensional Fatigue Inventory (MFI) Fatigue was a primary outcome
Effectiveness results	At baseline, MFI general scores were 14.7 for the ETN group and 15.0 for the PBO group, which were worse than the population norms of 6.6 to 8.0. All MFI items demonstrated improvement from baseline after the double-blind period at Week 12 in both treatment groups with no statistically significant differences observed between groups. The MFI items largely remained steady in the ETN/ETN group through Week 24 over the course of the open-label period. MFI response improved in patients who switched from PBO to ETN treatment at Week 12 (no significant between-group differences) and reached a response at Week 24 that was comparable with those observed in patients who continued with ETN.
Safety results	During the double-blind period,treatment-emergent adverse events were reported in 63 of 111 patients in the etanercept group (57%) and 51 of113 in the placebo group (45%). In the open-label period, such events were reported in 35 of 102 patients in the etanercept/etanercept group (34%) and in 53 of 106 in the placebo/etanercept group (50%). There were no significant between-group differences in the frequency of grade 3 or 4 elevations in any of the laboratory parameters assessed during the double-blind period.
Main results	At baseline, Multidimensional Fatigue Inventory (MFI; ETN mean 14.7, PBO mean 15.0), EQ-5D utility (0.52, 0.57), EQ-5D visual analog scale (56.5, 56.4), and Medical Outcomes Study (MOS) Sleep Index II (45.5, 48.1) were worse than population norms (6.6–8.0, 0.86, 82.5, and 25.8, respectively). At Week 12, Bath AS Patient Global Score, nocturnal and average back pain, MOS Short Form-36 (SF-36) physical component, and Work Productivity and Activity Index (WPAI) presenteeism and activity impairment favored ETN ($p<0.05$). Nonsignificant improvements for ETN were seen in other WPAI domains, MFI, MOS-Sleep Index I and II, Hospital Anxiety and Depression Scale, EQ-5D utility score, and SF-36 mental component ($p>0.05$). At Week 24, patients in the PBO group who had switched to ETN at Week 12 showed improvement in most QOL assessments, similar to that seen in patients receiving ETN for 24 weeks.
Follow-up	24 weeks
Conclusions	Improvements favored ETN in QOL and productivity measures, with limited improvement on general QOL measures. Short disease duration, a short PBO-controlled period, and a wide range of QOL scores at baseline may have influenced improvements.

Emery et al., 2006	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=465) ≈ Female, %: Rituximab 2 1,000-mg infusions group: 80, Rituximab 2 5000-mg infusions group: 83, Placebo group: 80 ≈ Age, years: Rituximab 2 1,000-mg infusions group: 51.1, Rituximab 2 5000-mg infusions group: 51.4, Placebo group: 51.1 ≈ Disease duration, years: Rituximab 2 1,000-mg infusions group: 9.3, Rituximab 2 5000-mg infusions group: 11.1, Placebo group: 10.8 Diagnosed according to the American College of Rheumatology (ACR) revised criteria
Intervention(s)	Rituximab
Intervention(s) characteristics	A total of 465 patients were randomized into 9 treatment groups: 3 rituximab groups (placebo [n=149], 500 mg [n=124], or 1,000 mg [n=192] on days 1 and 15) each also taking either placebo glucocorticoids, intravenous methylprednisolone premedication, or intravenous methylprednisolone premedication plus oral prednisone for 2 weeks. All patients received MTX (10–25 mg/week); no other DMARDs were permitted. Rituximab was administered by intravenous (IV) infusion in RF-positive patients: placebo, 500 mg or 1,000 mg on days 1 and 15 (total dose 0 mg, 1,000 mg, and 2,000 mg). Glucocorticoids were administered as placebo methylprednisolone, given IV 30–60 minutes before the infusion of rituximab (or rituximab placebo) on days 1 and 15, premedication methylprednisolone 100 mg, given IV on days 1 and 15 (250 mg prednisone equivalent), or premedication methylprednisolone 100 mg, given IV on days 1 and 15 plus 60 mg of oral prednisone on days 2–7 and 30 mg on days 8–14 (total glucocorticoid dose 820 mg prednisone equivalent). RF-negative patients received either placebo or rituximab (2 1,000-mg infusions), with or without glucocorticoids. All patients received a weekly regimen of MTX (10–25 mg orally or parenterally) with folate (±5 mg/week).
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Changes in fatigue, measured as the percentage improvement in the FACIT-F score between baseline and week 24, were 20% and 28% in the rituximab 2 500-mg and 2 1,000-mg infusions groups, respectively, compared with 4% in the placebo group. In both rituximab groups, the mean change from baseline in the FACIT-F score exceeded 4 points, which is the minimum clinically important difference. This was not the case in the placebo group.
Safety results	Both dosages of rituximab were generally well tolerated, with a low incidence of serious adverse events, including serious infections. The majority of adverse events were infusion associated, mild to moderate in intensity, and easily managed. Premedication with IV glucocorticoids did, however, reduce the incidence and severity of infusion-associated events following the first infusion of rituximab. The incidence of reactions following the second infusion was low in all groups, with 2 weeks of oral glucocorticoid treatment providing no additional safety benefit over IV glucocorticoid premedication alone.
Main results	Significantly more patients who received 2 500-mg or 2 1,000-mg infusions of rituximab met the American College of Rheumatology 20% improvement criteria (achieved an ACR20 response) at week 24 (55% and 54%, respectively) compared with placebo (28%; $p<0.0001$). ACR50 responses were achieved by 33%, 34%, and 13% of patients, respectively ($p<0.001$), and ACR70 responses were achieved by 13%, 20%, and 5% of patients ($p<0.05$). Changes in the Disease Activity Score in 28 joints (-1.79, -2.05, -0.67; $p<0.0001$) and moderate to good responses on the European League Against Rheumatism criteria ($p<0.0001$) reflected the ACR criteria responses. Glucocorticoids did not contribute significantly to the primary efficacy end point, ACR20 response at 24 weeks. Intravenous glucocorticoid premedication reduced the frequency and intensity of first infusion–associated events; oral glucocorticoids conferred no additional safety benefit. Rituximab was well tolerated; the type and severity of infections was similar to those for placebo.
Follow-up	24 weeks
Conclusions	Both rituximab doses were effective and well tolerated when added to MTX therapy in patients with active RA. The primary end point (ACR20 response) was independent of glucocorticoids, although intravenous glucocorticoid premedication improved tolerability during the first rituximab infusion.

Fleischmann et al., 2009	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=220) ≈ Female, %: Certolizumab pegol 400 mg group: 78.4, Placebo group: 89 ≈ Age, years: Certolizumab pegol 400 mg group: 52.7, Placebo group: 54.9 ≈ Disease duration, years Certolizumab pegol 400 mg group: 8.7, Placebo group: 10.4 Diagnosed with 1987 American College of Rheumatology (ACR) criteria
Intervention(s)	Certolizumab pegol
Intervention(s) characteristics	This study evaluated the efficacy and safety of certolizumab pegol 400 mg, a novel, poly- (ethylene glycol) (PEG)ylated, Fc-free TNFa inhibitor, as monotherapy in patients with active RA. 220 patients previously failing >1 disease-modifying antirheumatic drug (DMARD) were randomised 1:1 to receive subcutaneous certolizumab pegol 400 mg (n=111) or placebo (n=109) every 4 weeks.
Control	Placebo
Outcomes of interest (types and measuring instruments)	11-point Fatigue Assessment Scale (FAS) Fatigue was a secondary outcome
Effectiveness results	Statistically significant and clinically meaningful improvements in FAS scores were achieved throughout the 24-week study: least squares mean change from baseline in FAS was 21.69 for certolizumab pegol vs 20.27 for placebo at week 24 (p,0.001). At week 24, 46% of patients treated with certolizumab pegol reported improvements in fatigue of >MCID vs 17% for placebo (p,0.001).
Safety results	Treatment-emergent AEs occurred in 57.8% and 75.7% of patients in the placebo and certolizumab pegol groups, respectively. The majority of AEs in both treatment groups were mild or moderate.
Main results	At week 24, the ACR20 response rates were 45.5% for certolizumab pegol 400 mg every 4 weeks vs 9.3% for placebo (p<0.001). Differences for certolizumab pegol vs placebo in the ACR20 response were statistically significant as early as week 1 through to week 24 (p<0.001). Significant improvements in ACR50, ACR components, DAS28(ESR)3 and all patient-reported outcomes were also observed early with certolizumab pegol and were sustained throughout the study. Most adverse events were mild or moderate and no deaths or cases of tuberculosis were reported.
Follow-up	24 weeks
Conclusions	Treatment with certolizumab pegol 400 mg monotherapy every 4 weeks effectively reduced the signs and symptoms of active RA in patients previously failing >1 DMARD compared with placebo and demonstrated an acceptable safety profile.

Genovese et al., 2007	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=100) ≈ Female, %: Adalimumab group: 43, Placebo group: 49 ≈ Age, years: Adalimumab group: 50.4, Placebo group: 47.7 ≈ Disease duration, years: Adalimumab group: 7.5, Placebo group: 7.2
Intervention(s)	Adalimumab 40 mg (subcutaneous injections, every other week)
Intervention(s) characteristics	Active PsA in patients who had had an inadequate response to DMARD therapy. Following a screening period of up to 14 days, patients were stratified by DMARD use at baseline (yes/no), then randomized in a 1:1 ratio to receive a subcutaneous injection of adalimumab 40 mg every other week (eow) or placebo for 12 weeks.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	During the first 12 weeks of therapy, the FACIT-F scores of the 2 treatment groups improved by similar amounts, although each increased by < 4 units, the amount needed to be clinically meaningful. For patients from the placebo and adalimumab arms, the mean improvements in the FACIT-F scores from baseline to Week 24 were 5.6 and 2.9, respectively, and the mean changes in the DLQI were –3.9 and –3.5.
Safety results	The incidence of AE reported during the 12 weeks of double-blind therapy was statistically significantly lower for adalimumab (52.9%) compared to placebo (79.6%) (p≤0.01). During the first 12 weeks, most AE were mild or moderate, and there were 3 serious AE and 3 AE that led to study discontinuation. During the open-label period of study, the rates of AE (54.6%), serious AE (3.1%), and AE leading to discontinuation of adalimumab (6.2%) were consistent with those observed during the double-blind period.
Main results	At Week 12, an ACR20 response was achieved by 39% of adalimumab patients vs 16% of placebo patients (p=0.012), and a PsARC response was achieved by 51% with adalimumab vs 24% with placebo (p=0.007). At Week 12, measures of skin lesions and disability were statistically significantly improved with adalimumab. After Week 12, open-label adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR20 response rates of 65% and 57%, respectively, observed at Week 24. Serious adverse events had similar frequencies during therapy with placebo (4.1%), blinded adalimumab (2.0%), and open-label adalimumab (3.1%). No serious infections occurred during adalimumab therapy.
Follow-up	12 weeks
Conclusions	In this study of patients who had active PsA and a previous, inadequate response to DMARD therapy, adalimumab was well tolerated and significantly reduced the signs, symptoms, and disability of PsA during 12 weeks of blinded and 12 weeks of open-label therapy. Adalimumab also improved psoriasis in these patients.

Genovese et al., 2008	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=317) ≈ Female, %: Abatacept group: 43, Placebo group: 49 ≈ Age, years: Abatacept group: 50.4, Placebo group: 47.7 ≈ Disease duration, years: Abatacept group: 7.5, Placebo group: 7.2
Intervention(s)	Abatacept 10 mg/kg
Intervention(s) characteristics	Patients completing the 6-month, double-blind period were eligible to enter the long-term extension; patients received abatacept ,10 mg/kg, plus diseasemodifying antirheumatic drugs. Patients had active RA and an inadequate response to anti-TNF therapy due to lack of efficacy (either etanercept or infliximab or both (administered sequentially).
Control	Placebo
Outcomes of interest (types and measuring instruments)	VAS-fatigue Fatigue was a secondary outcome
Effectiveness results	At 2 years, mean reduction from baseline (standard errors) in fatigue VAS was -28.2 (2.1) for patients originally randomised to abatacept, compared with -25.0 (2.0) at 6 months. Improvements exceeded the minimal clinically important difference of 10 for fatigue. For patients originally randomised to placebo, reduction in fatigue comparable with the original abatacept group was observed at 2 years; -21.5 (3.7).
Safety results	During the double-blind period, a similar frequency of both AEs and SAEs was observed in the abatacept and placebo groups throughout 6 months of treatment. The types of AEs, including infusional events, were generally similar to those reported during the double-blind period.
Main results	317 patients (218 from the abatacept and 99 from the placebo group) entered and 222 (70%) completed 18 months of long-term extension treatment. The incidence and type of adverse events were consistent between the double-blind and cumulative (double-blind plus long-term extension) periods. Rates of serious adverse events were 25.6 and 23.4 per 100 patient-years in the double-blind vs cumulative period. At 6 months and 2 years, using non-responder analyses, ACR responses in abatacept-treated patients were: ACR 20, 59.4% and 56.2%; ACR 50, 23.5% and 33.2%; ACR 70, 11.5% and 16.1%; HAQ-DI responses were 54.4% and 47.9%. At 6 months and 2 years, using post-hoc as observed analyses, the percentage of patients (95% confidence interval) achieving DAS28 (C-reactive protein) low disease activity score (3.2) and DAS28 (C-reactive protein)-defined remission (2.6) increased from 18.3% (13.0 to 23.5) to 32.0% (24.6 to 39.4) and 11.1% (6.8 to 15.3) to 20.3% (13.9 to 26.6). Clinically meaningful improvements in SF-36, pain, fatigue and sleep problems were also maintained throughout the 2 years of abatacept treatment.
Follow-up	2 years
Conclusions	No unique safety observations were reported during open-label exposure. Improvements in the signs and symptoms of rheumatoid arthritis, physical function and health-related quality of life observed after 6 months, were maintained throughout the 2 years in this population with difficult-to-treat disease.

Genovese et al., 2012	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=444) ≈ Female, %: Placebo + MTX group: 82, Golimumab 100 mg + Placebo group: 78.9, Golimumab 50 mg + MTX group: 80.9, Golimumab 100 mg + MTX group: 80.9 ≈ Age, years: Placebo + MTX group: 51.2, Golimumab 100 mg + Placebo group: 50, Golimumab 50 mg + MTX group: 50.3, Golimumab 100 mg + MTX group: 50 ≈ Disease duration, years: Placebo + MTX group: 8.6, Golimumab 100 mg + Placebo group: 8.3, Golimumab 50 mg + MTX group: 7.3, Golimumab 100 mg + MTX group: 9 Diagnosis of RA according to the revised 1987 criteria of the American College of Rheumatology (ACR)
Intervention(s)	Golimumab 50 mg + MTX, or golimumab 100 mg + MTX
Intervention(s) characteristics	444 patients were randomly assigned (3:3:2:2) to receive placebo injections plus MTX with crossover to golimumab 50 mg plus MTX at Week 24, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX, or golimumab 100 mg injections plus MTX. Injections were administered subcutaneously every 4 weeks through Week 48. At Week 16, patients who had < 20% improvement from baseline in both total tender and total swollen joint counts entered early escape in a double-blind fashion. Patients who originally received placebo plus MTX switched to golimumab 50 mg plus MTX, those who originally received golimumab 100 mg plus placebo switched to golimumab 100 mg plus MTX, and those who originally received golimumab 50 mg plus MTX switched to golimumab 100 mg plus MTX. Patients who were originally assigned to receive golimumab 100 mg plus MTX did not have any adjustment in treatment.
Control	Subcutaneous placebo + MTX (crossover to golimumab 50 mg at Week 24), golimumab 100 mg + placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue) Fatigue was a primary outcome
Effectiveness results	At Week 14, significantly greater mean (±SD) improvements from baseline in FACIT-F scores were observed in the golimumab 100 mg plus placebo group (6.08±10.81; p=0.002), the golimumab 50 mg plus MTX group (7.58±8.93; p<0.001), and the golimumab 100 mg plus MTX group (6.40±9.62; p=0.002) compared with the placebo plus MTX group (2.28±9.23). Similar findings were observed at Week 24. At both Weeks 14 and 24, the proportion of patients achieving a clinically meaningful improvement in the FACIT-Fatigue score was significantly higher in the golimumab 100 mg plus placebo group [60.9% (78/128), p<0.001, and 60.0% (75/125), p<0.05, respectively], the golimumab 50 mg plus MTX group [70.1% (61/87), p<0.001, and 62.5% (55/88),p<0.01, respectively], and the golimumab 100 mg plus MTX group [58.8% (50/85) and 63.2% (55/87), respectively; p<0.01 for both] compared with the placebo plus MTX group [38.8% (50/129) and 44.1% (56/127), respectively]. FACIT-F scores correlated with HAQ-DI scores at baseline (r=-0.55, p<0.0001), and improvement in FACIT-F scores correlated with improvements in HAQ-DI scores at both Week 14 (r=0.54, p<0.0001) and Week 24 (r=0.55, p<0.0001).
Safety results	Not stated
Main results	Mean improvements from baseline in HAQ-DI, SF-36 PCS, and FACIT-Fatigue scores (Weeks 14 and 24) were significantly greater for golimumab 50 mg + MTX and 100 mg + MTX vs placebo + MTX. Significantly greater proportions of patients treated with golimumab + MTX achieved clinically meaningful improvements from baseline to Weeks 14 and 24 in HAQ-DI, PCS, and FACIT-Fatigue scores. Mean improvements in SF-36 PCS (Week 14), MCS (Week 24), and FACIT-Fatigue (Weeks 14 and 24) scores were significantly greater for golimumab 100 mg + placebo vs placebo + MTX. Mean improvements from baseline in HAQ-DI, SF-36 PCS, and MCS scores through Week 24 were sustained through Week 52.
Follow-up	52 weeks
Conclusions	Patients with active RA despite MTX had significant improvement in physical function, general health, and fatigue following golimumab + MTX therapy; improvements in physical function and general health were maintained through Week 52.

Genovese et al., 2018	
Participants characteristics (number, age, disease criteria, details)	RA patients (MTX add-on study, n=594; Monotherapy study, n=293) ≈ Female, %: MTX add-on study: 81, Monotherapy study: 81.6 ≈ Age, years: MTX add-on study: 53.4, Monotherapy study: 52.1 ≈ Disease duration, years: MTX add-on study: 8.3, Monotherapy study: 8.8 Diagnosis of RA according to the 2010 ACR/European League Against Rheumatism criteria
Intervention(s)	Filgotinib 50 mg, 100 mg, or 200 mg
Intervention(s) characteristics	Patient were randomized to daily placebo or filgotinib 50 mg, 100 mg, or 200 mg as add-on therapy to MTX or as monotherapy. At week 12, nonresponders receiving filgotinib 50 mg in both studies or placebo in the add-on study, and all patients receiving placebo as monotherapy, were re-assigned to filgotinib 100 mg. randomization was stratified by geographical region and previous use of biologic DMARDs (bDMARDs) (to which < 10% of the total study population had been previously exposed).
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	In both studies, all treatment groups demonstrated numerical increases in FACIT-F scores over the course of the 24-week treatment period, indicating reduced fatigue. At week 24 in the MTX add-on study, scores had increased by 6.0 points in the placebo group and by 7.7–12.8 points in the filgotinib groups. Statistically significantly greater improvements vs placebo were observed from the first measured time point-week 4-for filgotinib 100 mg q.d. and 100 mg b.i.d.. By week 12, improvements in the filgotinib 200-mg q.d. group were also statistically significantly greater than in the placebo group and remained so until week 24. There was no significant improvement in FACIT-Fatigue scores vs placebo at any time point in the filgotinib 50-mg b.i.d., 50-mg q.d., or 25-mg b.i.d. treatment groups. In the monotherapy study, scores at week 12 were increased by 3.9 points in the placebo group and by 9.5– 11.2 points in the filgotinib groups; at week 24, scores in the filgotinib groups were 10.0–13.7 points higher than at baseline. Statistically significantly greater improvements vs placebo were observed at week 4 in the monotherapy study in all filgotinib groups; these improvements vs placebo were maintained until week 12 and FACIT-F scores continued to increase to week 24.
Safety results	Not stated
Main results	At week 12, improvements in all PROs, apart from the SF-36 mental component in the add-on study, were statistically better with filgotinib than placebo; some improvements were noted as early as the first assessment time point (week 1 or week 4). Filgotinib improved HAQ-DI by 0.58–0.84 points, FACIT-Fatigue by 6.9–11.4 points, Patient Global by 25.2–35.6 mm, and Pain by 24.2–37.9 mm; scores were maintained or improved to week 24. Across all PROs, more patients achieved minimal clinically important differences and normative values with filgotinib 200 mg than placebo. Patients re-assigned to filgotinib 100 mg at week 12 experienced improvements in PROs between weeks 12 to 24.
Follow-up	24 weeks
Conclusions	Filgotinib as MTX add-on therapy or as monotherapy demonstrated rapid and sustained (to 24 weeks) improvements in health-related quality of life and functional status in patients with active RA.

Genovese et al., 2019	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=448) ≈ Female 80.4% ≈ Age 56 years ≈ Disease duration, years: Filgotinib 200 mg group: 9.8, Filgotinib 100 mg group: 10.3, Placebo group: 9.9
Intervention(s)	Filgotinib, 200 mg or filgotinib 100 mg
Intervention(s) characteristics	Patients with moderately to severely active RA and inadequate response/intolerance to 1 or more prior bDMARDs. Filgotinib, 200 mg (n=148); filgotinib, 100 mg (n=153); or placebo (n=148) once daily; patients continued concomitant stable conventional synthetic DMARDs (csDMARDs). All patients assigned to once-daily filgotinib, 200 mg; filgotinib, 100 mg; or placebo continued 1 to 2 protocol-specified stable csDMARDs (methotrexate, hydroxychloroquine, sulfasalazine, or leflunomide; methotrexate and leflunomide were not permitted in combination), and dose decreases were permitted only for intolerance/AE and/or laboratory abnormalities but not for change in disease activity. Stable doses of glucocorticoids (≤10 mg/d prednisone or equivalent) and/or nonsteroidal anti-inflammatory drugs were permitted.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue Fatigue was a <u>secondary outcome</u>
Effectiveness results	Statistically significant effects were seen for improvement in FACIT-F scores with filgotinib, 200 mg. Difference of mean change of FACIT-fatigue from baseline vs placebo was 5.0 and 3.2 in 200 mg group (p<0.001) and 100 mg group (p=0.007), respectively.
Safety results	Treatment-emergent AEs were reported in 102 patients (69.4%) receiving filgotinib, 200 mg; 97 (63.4%) receiving filgotinib, 100 mg; and 100 (67.6%) receiving placebo; 30 (6.7%) were grade 3 or greater (by Common Terminology Criteria for Adverse Events) in severity. The most frequently reported AEs were nasopharyngitis, upper respiratory tract infection, nausea, bronchitis, and headache. Overall, serious AEs occurred in 6 patients (4.1%) receiving filgotinib, 200 mg; 8 (5.2%) receiving filgotinib, 100 mg; and 5 (3.4%) receiving placebo. AEs leading to study drug discontinuation were reported in 5 patients (3.4%) receiving filgotinib, 200mg; 6 (3.9%) receiving filgotinib, 100 mg; and 3 (2.0%) receiving placebo.
Main results	Among 448 patients who were treated (mean [SD] age, 56 [12] years; 360 women [80.4%]; mean [SD] DAS28-CRP score, 5.9 [0.96]; 105 [23.4%] with 3 prior bDMARDs), 381 (85%) completed the study. At week 12, more patients receiving filgotinib, 200 mg (66.0%) or 100 mg (57.5%), achieved ACR20 response (placebo, 31.1%; difference vs placebo: 34.9% [95% CI= 23.5% to 46.3%] and 26.4% [95% CI=15.0% to 37.9%], respectively; both p<0.001), including among patients with prior exposure to 3 or more bDMARDs (70.3%, 58.8%, and 17.6%, respectively; difference vs placebo: 52.6% [95% CI=30.3% to 75.0%] for filgotinib, 200 mg, and 41.2% [95% CI=17.3% to 65.0%] for filgotinib, 100 mg; both p<0.001). The most common adverse events were nasopharyngitis (10.2%) for filgotinib, 200 mg; headache, nasopharyngitis, and upper respiratory infection (5.9% each) for filgotinib, 100 mg; and RA (6.1%) for placebo. Four uncomplicated herpes zoster cases and 1 retinal vein occlusion were reported with filgotinib; there were no opportunistic infections, active tuberculosis, malignancies, gastrointestinal perforations, or deaths.
Follow-up	24 weeks
Conclusions	Among patients with active RA who had an inadequate response or intolerance to 1 or more bDMARDs, filgotinib, 100 mg daily or 200 mg daily, compared with placebo resulted in a significantly greater proportion achieving a clinical response at week 12. However, further research is needed to assess longer-term efficacy and safety.

Ghiti Moghadam et al., 2018	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=817) ≈ Female, %: Stop TNFi group: 68.2, Continue TNFi group: 66 ≈ Age, years: Stop TNFi group: 60, Continue TNFi group: 59.7 ≈ Disease duration, years: Stop TNFi group: 12, Continue TNFi group: 11.1 Diagnosis of RA according to the 1987 ACR criteria
Intervention(s)	Stopping tumor necrosis factor inhibitor (TNFi) treatment
Intervention(s) characteristics	RA patients with ≥6 months of remission or stable low disease activity were randomized 2:1 to stopping or continuing TNFi. In case of flare, TNFi was restarted at the discretion of the rheumatologist.
Control	Continue TNFi
Outcomes of interest (types and measuring instruments)	Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) Fatigue was a secondary outcome
Effectiveness results	Stopping TNFi had a significant, but small, short-term negative impact on fatigue (in 3 months: p=0.003, in 6 months: p<0.001, in 9 months: p<0.001, and in 12 months: p<0.001).
Safety results	Not stated
Main results	TNFi was restarted within 12 months in 252 of 531 patients (47.5%) in the stop group. At 3 months, mean PRO scores were significantly worse in the stop group, and a larger proportion of patients experienced a minimum clinically important difference (MCID) on all PROs. Effect sizes (ES) were strongest for health utility (ES -0.24) and pain (ES -0.30). Mean scores improved again after this point, but disability scores remained significantly different at 12 months. After 12 months, the relative risk of experiencing an MCID ranged from 1.16 for mental health status to 1.58 for fatigue. Mean PRO scores for patients restarting TNFi within 6 months were no longer significantly different from those that did not restart TNFi at 12 months.
Follow-up	12 months
Conclusions	Stopping TNFi had a significant negative short-term impact on a broad range of PROs. Long-term negative consequences appeared to be limited, and outcomes in patients needing to restart TNFi within the first 6 months tended to be restored at 12 months.

Gladman et al., 2007	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=313) ≈ Female, %: Adalimumab group: 43.7, Placebo group: 45.1 ≈ Age, years: Adalimumab group: 48.6, Placebo group: 49.2 ≈ Disease duration, years: Adalimumab group: 9.8, Placebo group: 9.2
Intervention(s)	Adalimumab
Intervention(s) characteristics	Patients with moderately- to severely- active PsA were treated with adalimumab, 40 mg, every other week, or placebo. After 12 weeks, patients who failed to have at least a 20% decrease in both swollen and tender joint counts on two consecutive visits could receive rescue treatment with corticosteroids or disease-modifying antirheumatic drugs. All patients who completed the double-blind study were eligible for long-term treatment in an ongoing, open-label extension study.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	The mean changes from baseline in FACIT-Fatigue were significantly greater for patients treated with adalimumab than placebo at weeks 12 and 24 ($p<0.001$ for both weeks). At week 12, 60.7% of patients treated with adalimumab and 30.4% of those treated with placebo achieved or surpassed the MCID of a four-point change. These results were similar at week 24 ($p<0.001$ for both weeks).
Safety results	Adalimumab was generally well-tolerated during the 24-week trial, with a similar incidence of adverse events compared with that in the placebo group. Common adverse events were similar to those seen in clinical trials involving patients with RA or were thought to be related to underlying disease. Twelve patients experienced serious adverse events, 7 of whom were taking placebo and 5 of whom were taking adalimumab. Serious adverse events in the placebo-treated patients were cerebrovascular accident, pericarditis and hand fracture in the same patient, muscle weakness, deep venous thrombosis, and pulmonary embolism in the same patient, depression, 2 events of hyperglycemia in the same patient, cellulitis, and aggravation of coronary artery disease.
Main results	Adalimumab (n=151) and placebo (n=162) groups were comparable with respect to baseline demographics and disease severity. Significant changes from baseline in HAQ DI were reported for adalimumab v placebo (-0.4 vs -0.1, $p<0.001$) at both 12 and 24 weeks. At week 24, significant improvements in the SF-36 domains of physical functioning, role-physical, bodily pain, general health, vitality and social functioning, as well as the physical component summary score, were observed for adalimumab vs placebo ($p<0.01$). These reported changes in HAQ DI and SF-36 were also clinically important. Significantly more patients treated with adalimumab had complete resolution of functional loss (HAQ DI=0) and dermatological-related functional limitations (DLQI=0) compared with placebo at weeks 12 and 24 ($p\leq0.001$). Adalimumab led to significantly greater improvements in FACIT-Fatigue scores, pain scores, and disease activity measures vs placebo at 12 and 24 weeks ($p<0.001$ for all).
Follow-up	24 weeks
Conclusions	Adalimumab improved physical-related and dermatological-related functional limitations, HRQOL, fatigue and pain in patients with PsA treated for 24 weeks.

Gladman et al., 2014	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=409) ≈ Female, %: CZP 400 mg every 4-week group: 54.1, CZP 200 mg every 2-week group: 53.6, Placebo group: 58.1 ≈ Age, years: CZP 400 mg every 4-week group: 47.1, CZP 200 mg every 2-week group: 48.2, Placebo group: 47.3 ≈ Disease duration, years: not stated Defined by the criteria of the Classification of Psoriatic Arthritis Study Group
Intervention(s)	Certolizumab pegol (CZP)
Intervention(s) characteristics	Patients were randomized 1:1:1 to placebo every 2 weeks or CZP 400 mg at weeks 0, 2, and 4, followed by either CZP 200 mg every 2 weeks or CZP 400 mg every 4 weeks.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue Assessment Scale (FAS) Fatigue was a secondary outcome
Effectiveness results	Fatigue was substantially reduced in the CZP groups compared to placebo from week 2 ($p \leq 0.05$) to week 24 ($p < 0.001$). At week 24, more CZP-treated patients reported improvements greater than or equal to the g minimum clinically important difference (MCID) for fatigue compared to the placebo group ($p < 0.001$), with differences observed between CZP 200 mg every 2 weeks and CZP 400 mg every 4 weeks patients vs placebo patients from week 1 onward (50.7% and 42.2% vs 33.8%, respectively).
Safety results	Rates of adverse events (AEs), serious AEs, and infections were similar between treatment groups through week 24. The most common non-infectious AEs were diarrhoea (3.6% CZP vs 2.9% placebo) and headache (3.6% CZP vs 1.5% placebo). The most common infectious AEs were nasopharyngitis (8.7% CZP vs 7.4% placebo) and upper respiratory tract infection (7.8% CZP vs 5.1% placebo). Most AEs were mild to moderate in severity. No individual type of serious AE occurred in more than one patient. Increases in liver enzymes were reported more frequently in CZP patients.
Main results	A total of 409 patients were randomized. Twenty percent had received a prior TNF inhibitor. Baseline demographics were similar between the treatment groups. At week 24, clinically meaningful differences in HAQ DI, SF-36, PsAQOL, fatigue, pain, and DLQI were observed in both CZP arms vs placebo ($p < 0.001$), irrespective of prior TNF inhibitor exposure. More CZP-treated patients reached SF-36 general population norms than placebo-treated patients.
Follow-up	24 weeks
Conclusions	Both CZP dosing schedules provided rapid improvements in PROs across multiple disease aspects in patients with PsA. The benefits of CZP treatment for health-related quality of life were seen across generic, PsA-specific, and dermatology-specific measures and were observed in patients regardless of prior TNF inhibitor exposure.

Gottenberg et al., 2014	
Participants characteristics (number, age, disease criteria, details)	Primary Sjögren syndrome (pSS) patients (n=409) ≈ Female, %: hydroxychloroquine group: 89.3, Placebo group: 93.8 ≈ Age, years: hydroxychloroquine group: 56.3, Placebo group: 55.6 ≈ Disease duration, years (median): hydroxychloroquine group: 1, Placebo group: 1 Fulfill the American-European Consensus Group Criteria for primary Sjögren syndrome
Intervention(s)	Hydroxychloroquine
Intervention(s) characteristics	Patients were randomized (1:1) to receive hydroxychloroquine (400 mg/d) or placebo until week 24. All patients were prescribed hydroxychloroquine between weeks 24 and 48. The primary end point was the proportion of patients with a 30% or greater reduction between weeks 0 and 24 in scores on 2 of 3 numeric analog scales (from 0 [best] to 10 [worst]) evaluating dryness, pain, and fatigue.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue - VAS Fatigue was a primary outcome
Effectiveness results	At 24 weeks, the proportion of patients meeting the primary end point (≥30% reduction in 2 of the 3 numeric analog scale scores) was 17.9% (10/56) in the hydroxychloroquine group and 17.2% (11/64) in the placebo group (OR=1.01; 95% CI=0.37 to 2.78; p=0.98 after multiple imputation). Between weeks 0 and 24, the mean (SD) numeric analog scale for fatigue changed from 6.26 (2.27) to 5.72 (2.38) in the placebo group and 6.00 (2.52) to 5.94 (2.40) in the hydroxychloroquine group. Fatigue scores did not differ between weeks 24 and 48 for patients receiving placebo who were prescribed hydroxychloroquine during the open extension phase. In a post hoc analysis, the minimally clinically important improvement scores for fatigue numeric analog scale scores were −2 points on the 10-point scales.
Safety results	During the first 24 weeks, there were 2 serious adverse events in the hydroxychloroquine group and 3 in the placebo group. In the last 24 weeks, there were 3 in the hydroxychloroquine group and 4 in the placebo group. One patient who received placebo died from pneumococcal meningitis.
Main results	At 24 weeks, the proportion of patients meeting the primary end point was 17.9% (10/56) in the hydroxychloroquine group and 17.2% (11/64) in the placebo group (OR=1.01; 95% CI=0.37-2.78; p=0.98). Between weeks 0 and 24, the mean (SD) numeric analog scale score for dryness changed from 6.38 (2.14) to 5.85 (2.57) in the placebo group and 6.53 (1.97) to 6.22 (1.87) in the hydroxychloroquine group. The mean (SD) numeric analog scale score for pain changed from 4.92 (2.94) to 5.08 (2.48) in the placebo group and 5.09 (3.06) to 4.59 (2.90) in the hydroxychloroquine group. The mean (SD) numeric analog scale for fatigue changed from 6.26 (2.27) to 5.72 (2.38) in the placebo group and 6.00 (2.52) to 5.94 (2.40) in the hydroxychloroquine group. All but 1 patient in the hydroxychloroquine group had detectable blood levels of the drug. Hydroxychloroquine had no efficacy in patients with anti-SSA autoantibodies, high IgG levels, or systemic involvement. During the first 24 weeks, there were 2 serious adverse events in the hydroxychloroquine group and 3 in the placebo group; in the last 24 weeks, there were 3 serious adverse events in the hydroxychloroquine group and 4 in the placebo group
Follow-up	48 weeks
Conclusions	Among patients with primary Sjögren syndrome, the use of hydroxychloroquine compared with placebo did not improve symptoms during 24 weeks of treatment. Further studies are needed to evaluate longer-term outcomes.

Hammoudeh et al., 2013	
Participants characteristics (number, age, disease criteria, details)	AS patients (n=1283) ≈ Female 25.4% ≈ Age (at disease onset) 32 years ≈ Disease duration 9 years Fulfill the modified New York criteria
Intervention(s)	Etanercept
Intervention(s) characteristics	Data were combined from four clinical trials for patients with AS who received at least one dose of etanercept, sulfasalazine or placebo and had at least one postbaseline assessment value. A week-12 endpoint was selected for the pooled analysis as it was shared by all four trials. Data for the etanercept 50-mg weekly and 25-mg twiceweekly dosing groups were combined to create one etanercept treatment group for analysis.
Control	Sulfasalazine or placebo
Outcomes of interest (types and measuring instruments)	Fatigue–VAS, BASDAI-fatigue item Fatigue was a primary outcome
Effectiveness results	Etanercept provided significantly greater improvements from baseline to week 12 in fatigue than either sulfasalazine or placebo. Fatigue significantly improved in the etanercept group, by 45%, compared with 26% and 13% of the sulfasalazine and placebo groups, respectively ($p<0.0001$); this represented a mean change from baseline of -27.5, -15.4 and -8.0, respectively. Improvement in fatigue in the etanercept group was significant after controlling for change in nocturnal back pain but was not significant in the sulfasalazine group.
Safety results	Not stated
Main results	Out of 1283 patients (etanercept, n=867; sulfasalazine, n=187; placebo, n=229), improvement in nocturnal back pain was a significant predictor of improvement in fatigue. Significant correlations were found between nocturnal back pain and fatigue, but not CRP levels. Etanercept provided significantly greater pain/fatigue improvement than sulfasalazine or placebo. Improvements in nocturnal back pain and fatigue had weak relationships with improvement in inflammation (CRP level).
Follow-up	12 weeks
Conclusions	AS patients treated with etanercept demonstrated superior improvement in nocturnal back pain and fatigue vs sulfasalazine or placebo. Decrease in nocturnal back pain can improve fatigue. Assessing treatment response using CRP levels alone may be misleading without also examining patient-reported outcomes such as back pain and fatigue.

Hartkamp et al, 2010	
Participants characteristics (number, age, disease criteria, details)	SLE patients (n=1283) ≈ Female 100% ≈ Age, years: DHEA group: 45, Placebo group: 41 ≈ Disease duration, years: DHEA group: 13, Placebo group: 12 Fulfilment of at least four American College of Rheumatology (ACR) SLE classification criteria
Intervention(s)	Dehydroepiandrosterone (DHEA)
Intervention(s) characteristics	60 female patients with inactive SLE received 200 mg oral DHEA or placebo.
Control	Placebo
Outcomes of interest (types and measuring instruments)	General fatigue scale of the Multidimensional Fatigue Inventory (MFI, range 4–20) Fatigue was a primary outcome
Effectiveness results	General fatigue showed a significant change for both treatments (p<0.001): the best scores were observed during treatment.
Safety results	Androgenic side effects and disease exacerbations occurred more often with DHEA (n=5) than placebo (n=2)
Main results	Patients from the DHEA and placebo group improved on general fatigue (p<0.001) and mental wellbeing (p=0.04). There was no differential effect of DHEA. The belief that DHEA had been used was a stronger predictor for improvement of general fatigue than the actual use of DHEA (p=0.04).
Follow-up	18 months
Conclusions	The trial does not indicate an effect of daily 200 mg oral DHEA on fatigue and well-being, and therefore DHEA treatment is not recommended in unselected female patients with quiescent SLE.

Hartkamp et al, 2008	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren syndrome (pSS) patients (n=1283) ≈ Female 100% ≈ Age, years: DHEA group: 55, Placebo group: 52 ≈ Disease duration, years: DHEA group: 8, Placebo group: 6 Fulfilled the European criteria for classification of pSS
Intervention(s)	Dehydroepiandrosterone (DHEA)
Intervention(s) characteristics	Patients with pSS randomly assigned to receive 200 mg oral DHEA or placebo.
Control	Placebo
Outcomes of interest (types and measuring instruments)	General fatigue scale of the Multidimensional Fatigue Inventory (MFI, range 4–20) Fatigue was a primary outcome
Effectiveness results	General fatigue showed a significant change for both treatments ($p<0.001$): it decreased during the first 6 months of medication use and steadily increased after this period. There was no differential effect of medication: the change in fatigue did not differ for the DHEA and placebo group ($p=0.77$).
Safety results	An increase of acne and body hair was reported more often by patients on DHEA than those on placebo: 37, 47, and 43% of the patients on DHEA reported an increase of acne at the 3, 6, and 12 month assessments (10, 7, and 10% of the patients on placebo) and 20, 40, and 63% of the patients on DHEA reported an increase of body hair (0, 3, and 7% of the patients on placebo). The frequencies of menstrual abnormalities and oily skin or capital hair did not differ between the groups with increased oily skin or capital hair after 12 months (17% in DHEA and 0% in placebo) as the only exception. One patient of the DHEA group stopped study medication after 3 months because she feared increase of hirsutism. In the DHEA group one patient stopped participation after 7 days because she experienced restlessness, malaise, night sweats, and skin rash and another patient stopped after 6 months, because of increased ocular pain and dryness, restlessness, and sleep disturbance.
Main results	Patients from both the DHEA and placebo treated group improved on general fatigue ($p<0.001$), mental well-being ($p=0.04$), and depressive mood ($p=0.008$). Physical functioning did not change ($p=0.44$). Of the secondary outcome variables, complaints of a dry mouth diminished during treatment in both groups ($p=0.006$), the erythrocyte sedimentation rate showed a decrease for the DHEA group ($p=0.02$), and complaints of dry eyes improved in the placebo group ($p=0.01$). The belief to have used DHEA was a stronger predictor for improvement of fatigue and well-being than the actual use of DHEA.
Follow-up	18 months
Conclusions	Our study does not support a superior effect of DHEA over placebo in female patients with pSS. Both DHEA and placebo induce improvement of fatigue and well-being. This may suggest possibilities for cognitive behavioural interventions.

Jenks et al., 2010	
Participants characteristics (number, age, disease criteria, details)	SpA patients (n=63) ≈ Female 37% ≈ Age 43.3 years ≈ Disease duration 8.9 years Patients meeting the European Spondylarthropathy Study Group (ESSG) criteria for SpA
Intervention(s)	Probiotic Therapy
Intervention(s) characteristics	The probiotic preparation contained 3 strains of bacteria, which contributed 5.5% of the weight of the powder composition. The remainder of the formulation consisted of the excipient ingredients, identical to placebo. The strains used in the active treatment were Streptococcus salivarius K12 (1 x 108 cfu/g), Bifidobacterium lactis LAFTI B94 (4 x 108 cfu/g), and Lactobacillus acidophilus LAFTI L10 (4 x 108 cfu/g). The placebo consisted of glucidex 37.6%, trehalose 56.49%, and vanilla flavor 0.43% and was identical in appearance, taste, and texture to the active probiotic treatment. Both probiotic and placebo were formulated by BLIS Technologies. BLIS Technologies had no involvement in study funding, study design, patient assessment, or statistical analysis. Participants were provided with a small plastic spoon and instructed to take one level spoonful (approximately 0.8 g) by mouth twice daily for 12 weeks. They were advised to keep the study drug in a cool dark place, but not necessarily to refrigerate. At baseline, Week 4, and Week 8 patients were given a fresh supply of probiotic or placebo and any remaining study drug from the preceding 4 weeks was collected to monitor compliance.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Multidimensional Assessment of Fatigue with total Global Fatigue Index (MAF-GFI) Fatigue was a primary outcome
Effectiveness results	MAF showed improvement in both groups during the study, but there was no statistically significant.
Safety results	A total of 26 patients reported adverse events, 14/32 (43.8%) in the probiotic group and 12/31 (38.7%) of those taking placebo. There were no serious adverse events reported and none required discontinuation of the study drug. The most common adverse event was a change in bowel habit, reported by 7 of those in the probiotic group and 6 in the placebo group.
Main results	Sixty-three patients were randomized to oral probiotic (n=32) or placebo (n=31). All patients completed the trial. No significant difference was noted between groups in any of the core domains. The mean BASFI fell from 3.5±2.0 to 2.9±1.9 in the probiotic group and from 3.6±1.9 to 3.1±2.2 in the placebo group (p=0.839). The mean BASDAI fell from 4.2±2.2 to 3.2±2.1 in the probiotic group and 4.5±2.0 to 3.9±2.2 in the placebo group (p=0.18). No significant adverse events were recorded in the probiotic-treated group.
Follow-up	12 weeks
Conclusions	In this randomized controlled trial, the probiotic combination administered did not demonstrate significant benefit over placebo, despite a theoretical rationale for this therapy.

Kekow et al., 2010	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=528) ≈ Female 73% ≈ Age 51 years ≈ Disease duration 9 months
Intervention(s)	Etanercept (ETN) 50 mg once weekly plus MTX
Intervention(s) characteristics	In period 1, patients were randomly assigned to one of two initial treatment groups, one receiving combination etanercept plus methotrexate and another receiving methotrexate alone. Participants received either etanercept 50 mg by subcutaneous injection or etanercept-matching placebo injections once a week for 52 weeks. Etanercept was given as two separate injections of 25 mg on the same day, once a week. All participants received oral methotrexate, starting at 7·5 mg once a week. In patients with tender or swollen joints, the dose was titrated up over 8 weeks to a maximum of 20 mg a week. After completion of 24 weeks of treatment, reductions in dose of prednisone or other oral corticosteroid by 1 mg per day or less were allowed every week. Oral corticosteroids were tapered to 3 mg per day or less before the dose of non-steroidal anti-inflammatory drug was decreased. All patients received folic acid supplementation of 5 mg twice weekly (not given on the same day as methotrexate) to reduce side-effects associated with methotrexate.
Control	MTX alone
Outcomes of interest (types and measuring instruments)	Fatigue VAS Fatigue was a primary outcome
Effectiveness results	Decreases in fatigue VAS scores (indicating improvement) were rapid and significantly greater for patients receiving ETN+MTX than patients receiving MTX ($p<0.001$), declining to almost half in the ETN+MTX group as early as week 2.
Safety results	246 (91.8%) patients in the methotrexate group and 247 (90.2%) in the combined-treatment group reported adverse events: the most common were nausea (50 [19%] in the methotrexate group and 53 [19%] in the combined treatment group) and nasopharyngitis (44 [16%] and 45 [16%]). Serious adverse events were recorded for 34 (12.7%) patients and 33 (12.0%). Serious adverse events occurring in more than one patient overall were worsening of rheumatoid arthritis (five patients in the methotrexate group and two in the combined-treatment group); breast cancer (three in the methotrexate group); chest pain (one in each group); pneumonia (one in each group); cholelithiasis (two in the combined-treatment group); intervertebral disc protrusion (two in the combined-treatment group); osteoarthritis (two in the methotrexate group); interstitial lung disease (two in the combined-treatment group); and hip arthroplasty (two in the methotrexate group).
Main results	Most PROs demonstrated significantly greater improvements with ETN+MTX than MTX alone, including physical functioning, pain, fatigue, and overall health status. A significantly greater improvement in HAQ score was observed in the ETN+MTX than the MTX group (21.02 vs 20.72; $p<0.001$) and a greater proportion reached the minimal clinically important difference of 0.22 (88% vs 78%; $p<0.006$). The relationship between PRO score and clinical status indicated that improvement was greatest among patients achieving remission.
Follow-up	2 years
Conclusions	Early treatment with ETN+MTX leads to significantly greater improvements in multiple dimensions of PROs than MTX alone. The close relationship between disease activity and PRO improvement suggests that early treatment, with remission as a goal, should maximise the chance of restoring normal functioning and HRQoL.

Keystone et al., 2008	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=499) ≈ Female 81% ≈ Age 52.5 years ≈ Disease duration 12 years Defined by the 1987 ACR (American College of Rheumatology) criteria
Intervention(s)	Rituximab (1,000 mg on days 1 and 15)
Intervention(s) characteristics	Patients had active disease and had failed treatment with 1 or more anti-TNF therapies. Patients were randomized at a ratio of 3:2 to receive rituximab (1,000 mg on days 1 and 15) or placebo. Both groups continued receiving stable doses of MTX (10-25 mg/week orally or parenterally) and received folate (5 mg/week or equivalent), intravenous methylprednisolone (100 mg 30 minutes before each infusion), and oral prednisone (60 mg on days 2-7, 30 mg on days 8-14) during the 2-week treatment period.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	The FACIT-F showed a significantly greater improvement in rituximab-treated patients compared with placebo-treated patients beginning at the first posttreatment assessment (week 12) and continuing through week 24 ($p<0.05$ for all time points from weeks 12-24). A significantly higher percentage of the rituximab group achieved an MCID on the FACIT-F scale at week 24 than patients in the placebo group ($p<0.0001$).
Safety results	Not stated
Main results	Rituximab patients had statistically significantly greater pain relief. The FACIT-F showed significantly greater improvement in rituximab patients than placebo patients from weeks 12 through 24. Mean improvement from baseline in functional disability (measured by the HAQ DI) was significantly greater in rituximab patients from weeks 8 to 24. The mean ± SD change from baseline for the SF-36 Physical Component Score was 6.64±8.74 for rituximab patients and 1.48±7.32 for placebo patients ($p<0.0001$). The mean change from baseline for the SF-36 Mental Component Score was 5.32±12.41 for rituximab patients and 2.25±12.23 for placebo patients ($p=0.03$).
Follow-up	24 weeks
Conclusions	Rituximab produced rapid, clinically meaningful, and statistically significant improvements in patient reported pain, fatigue, functional disability, health-related quality of life, and disease activity. These effects were sustained throughout the study.

Keystone et al., 2017	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=1305) ≈ Female, %: Baricitinib group: 77, Adalimumab group: 76, Placebo group: 78 ≈ Age, years: Baricitinib group: 54, Adalimumab group: 53, Placebo group: 53 ≈ Disease duration, 10 years
Intervention(s)	Baricitinib
Intervention(s) characteristics	Patients were randomised 3:3:2 to placebo (n=488), baricitinib 4mg once daily (n=487), or adalimumab 40mg biweekly (n=330) with background methotrexate. At week 24, patients receiving placebo switched to baricitinib. At week 16, patients whose tender and swollen joint counts improved from baseline by <20% at both weeks 14 and 16 were assigned rescue treatment (baricitinib 4mg). After week 16, patients could be rescued at investigators' discretion based on joint counts.
Control	Adalimumab 40mg biweekly or Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Treatment with baricitinib or adalimumab was associated with significant improvements in FACIT-F at the first assessment of the measure at week 4 (p≤0.001 for baricitinib vs placebo; p≤0.01 for adalimumab vs placebo). The improvements in the FACIT-F score were sustained to week 24 for both baricitinib and adalimumab vs placebo (p≤0.001) and were significant at weeks 20, 28 and 52 for baricitinib vs adalimumab (p≤0.05). For the FACIT-F, the percentage of patients who reported improvements that met or exceeded the MCID (≥3.56) was 59%, 66% and 68% for placebo, baricitinib and adalimumab, respectively (p≤0.05 for baricitinib vs placebo; p≤0.01 for adalimumab vs placebo), at week 12 and were 60% and 54% at week 52 for baricitinib and adalimumab, respectively (p=0.084). The percentage of patients who reported scores that met or exceeded the population normative value of ≥40.1 ranged from 41% to 46% for baricitinib and adalimumab at weeks 12 and 52.
Safety results	Not stated
Main results	Compared with placebo and adalimumab, baricitinib showed statistically significant improvements (p≤0.05) in HAQ-DI, PtGA, pain, FACIT-F, SF-36 physical component score, EQ-5D index scores and WPAI-RA daily activity at week 12. Improvements were maintained for measures assessed to week 52. Statistically significant improvement in patient diary measures (MJS duration and severity), worst tiredness and worst joint pain were observed for baricitinib vs placebo and adalimumab at week 12 (p≤0.05).
Follow-up	52 weeks
Conclusions	Baricitinib provided significantly greater improvement in most PROs compared with placebo and adalimumab, including physical function MJS, pain, fatigue, and quality of life. Improvement was maintained to the end of the study (week 52).

Khanna et al., 2016	
Participants characteristics (number, age, disease criteria, details)	Systemic sclerosis patients (n=87) ≈ Female, %: Tocilizumab group: 51, Placebo group: 48 ≈ Age, years: Tocilizumab group: 74, Placebo group: 80 ≈ Disease duration, months: Tocilizumab group: 17.6, Placebo group: 19.5 Patients met the 1980 American College of Rheumatology criteria for systemic sclerosis with no more than 5 years since their first non-Raynaud's sign or symptom and a modified Rodnan skin score of 15-40.
Intervention(s)	Tocilizumab
Intervention(s) characteristics	Tocilizumab is an interleukin 6 receptor-α inhibitor. This study assessed adults with progressive systemic sclerosis of 5 or fewer years' duration from first non-Raynaud's sign or symptom. Patients were randomly assigned (1:1) to weekly subcutaneous tocilizumab 162 mg or placebo.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	For FACIT-fatigue scores, the difference was not significant at 24 weeks or 48 weeks, but scores were better in the tocilizumab group than in the placebo group (Difference in means (95% CI) in FACIT-F between groups was –3.85 (–13.04 to 5.34, p=0.41) in week 24 and –8.30 (–19.31 to 2.71, p=0.14) in week 48).
Safety results	Overall, after 48 weeks of treatment, safety was consistent with the natural history of systemic sclerosis and the safety profile for tocilizumab.
Main results	We enrolled 87 patients: 43 assigned to tocilizumab and 44 assigned to placebo. The least squares mean change in modified Rodnan skin score at 24 weeks was -3.92 in the tocilizumab group and -1.22 in the placebo group (difference -2.70, 95% CI=-5.85 to 0.45; p=0.09). The least squares mean change at 48 weeks was -6.33 in the tocilizumab group and -2.77 in the placebo group (treatment difference -3.55, 95% CI=-7.23 to 0.12; p=0.05). In one of several exploratory analyses, fewer patients in the tocilizumab group than in the placebo group had a decline in percent predicted forced vital capacity at 48 weeks (p=0.03). However, we detected no significant difference in disability, fatigue, itching, or patient or clinician global disease severity. 42 (98%) of 43 patients in the tocilizumab group vs 40 (91%) of 44 in the placebo group had adverse events. 14 (33%) vs 15 (34%) had serious adverse events. Serious infections were more common in the tocilizumab group (seven [16%] of 43 patients) than in the placebo group (two [5%] of 44). One patient died in relation to tocilizumab treatment.
Follow-up	48 weeks
Conclusions	Tocilizumab was not associated with a significant reduction in skin thickening. However, the difference was greater in the tocilizumab group than in the placebo group and we found some evidence of less decline in forced vital capacity. The efficacy and safety of tocilizumab should be investigated in a phase 3 trial before definitive conclusions can be made about its risks and benefits.

Kruize et al., 1993	
Participants characteristics (number, age, disease criteria, details)	SjS patients (n=19) ≈ Female 100% ≈ Age 51.9 years ≈ Disease duration 3 years According to the criteria proposed by Daniels and Talal in 1987
Intervention(s)	Hydroxychloroquine
Intervention(s) characteristics	Patients were randomised (in blocks of four) to one of two treatment groups. The first group was treated with hydroxychloroquine for one year and with placebo during the second year. In the second group treatment was given in the reverse order. Hydroxychloroquine dosage was 400 mg daily, given in two tablets of 200 mg each. Placebo tablets, indistinguishable from hydroxychloroquine tablets, were also given twice daily.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue - patients were asked for the presence and severity compared with the previous visit. Fatigue was a secondary outcome
Effectiveness results	No significant differences were found in fatigue.
Safety results	One patient developed a moderate deterioration of liver function tests at the end of the first year in which she appeared to have been treated with hydroxychloroquine. Alkaline phosphatase increased from 72 to 179 (normal 27-93) IU/l, serum -y-glutamyltransferase from 6 to 87 (normal 7-29) IU/l, serum aspartate transaminase from 19 to 45 (normal <30) IU/1, serum alanine transaminase from 11 to 67 (normal <30) IU/l, whereas serum lactate dehydrogenase remained within the normal range. An expectative policy was followed. Liver function tests normalised within two months after cross over. No other side effect was noticed.
Main results	A significant decrease in IgG and IgM and a tendency for a decrease in the erythrocyte sedimentation rate (ESR) during treatment with hydroxychloroquine compared with treatment with placebo were found. No beneficial clinical effect of the use of hydroxychloroquine as expressed in preference for treatment with hydroxychloroquine or placebo regarding symptoms and signs of primary Sjogren's syndrome could be shown, however, nor any relevant change in tear gland activity and sequelae of peripheral tear function deficiency, nor salivary gland scintigraphy.
Follow-up	2 years
Conclusions	The use of hydroxychloroquine at a dose of 400 mg daily taken over a 12-month period does not have a worthwhile clinical benefit in patients with primary Sjogren's syndrome despite an improvement of hyperglobulinaemia and slight changes in the ESR and IgM.

Lai et al., 2012	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=36) ≈ Female 94% ≈ Age 44.6 years ≈ Disease duration: not stated
Intervention(s)	N-acetylcysteine (NAC)
Intervention(s) characteristics	N-acetylcysteine (NAC) is a glutathione (GSH) precursor. SLE patients were randomized to receive either placebo or NAC in 1 of 3 treatment arms of increasing doses: 600 mg, 1,200 mg, or 2,400 mg twice daily for 3 months. Twelve patients were enrolled in each dosing group; 9 received NAC while 3 received placebo.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue Assessment Scale (FAS) Fatigue was a secondary outcome
Effectiveness results	In the combined group of all SLE patients treated with NAC, the FAS score was improved from 28.5 at visit 1 to 24.1 at visit 3 (p=0.0006), 23.9 at visit 4 (p=0.005), and 24.8 at visit 5 (p=0.034). Mixed model analysis showed a reduction in the FAS score in NAC dosing group 2 relative to the placebo group (XTMIXED z=-2.08, p=0.038).
Safety results	None of the patients in dosing group 1 (NAC 1.2 gm/day; n=12) or dosing group 2 (NAC 2.4 gm/day; n=12) reported unpleasant smell or taste, and all 24 patients completed the treatment. Three patients dropped out of dosing group 3 (NAC 4.8 gm/day) due to heartburn after 19 days, nausea after 60 days, and nausea and headaches after 76 days. The third patient continued to take NAC after day 76 by reducing the original number of capsules to half and thus halving the original dosage to 2.4 gm/day. Since all 3 of the patients who reported intolerance were receiving NAC, in accordance with the Data Safety and Monitoring Plan, no higher dose was initiated.
Main results	NAC up to 2.4 gm/day was tolerated by all patients, while 33% of those receiving 4.8 gm/day had reversible nausea. Placebo or NAC 1.2 gm/day did not influence disease activity. Considered together, 2.4 gm and 4.8 gm NAC reduced the SLEDAI score after 1 month (p=0.0007), 2 months (p=0.0009), 3 months (p=0.0030), and 4 months (p=0.0046); the BILAG score after 1 month (p=0.029) and 3 months (p=0.009); and the FAS score after 2 months (p=0.0006) and 3 months (p=0.005). NAC increased Δm (p=0.0001) in all T cells, profoundly reduced mTOR activity (p=0.0009), enhanced apoptosis (p=0.0004), reversed expansion of CD4-CD8-T cells (mean ± SEM 1.35±0.12-fold change; p=0.008), stimulated FoxP3 expression in CD4+CD25+ T cells (p=0.045), and reduced anti-DNA production (p=0.049).
Follow-up	5 months
Conclusions	This pilot study suggests that NAC safely improves lupus disease activity by blocking mTOR in T lymphocytes.

Li et al., 2016	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=264) ≈ Female 81% ≈ Age 47 years ≈ Disease duration 7.8 years According to the American College of Rheumatology (ACR) 1987 revised criteria
Intervention(s)	Golimumab + methotrexate (MTX)
Intervention(s) characteristics	Eligible patients were randomly assigned (1:1) to receive subcutaneous injections of placebo (Group 1) or golimumab 50 mg (Group 2) at baseline and every 4 weeks thereafter; all patients continued to receive oral MTX (7.5-20 mg/week). Study drug injections were administered at baseline and every 4 weeks thereafter. Randomization was stratified using block methodology by investigational study site and by patients' screening CRP levels (≥15 or <15 mg/L). Adjustment of the MTX dose was allowed only if required because of MTX toxicity. Patients in Group 1 could enter blinded early escape to golimumab 50 mg at week 16 if they had < 20% improvement from baseline in tender and swollen joint counts; no golimumab dose changes were permitted for patients in Group 2. At week 24, all Group 1 patients who were still receiving placebo crossed over to receive golimumab 50 mg. The final golimumab injection was performed at week 48; final efficacy and safety assessments were conducted at week 52 and week 56, respectively.
Control	Placebo + MTX
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Significantly greater improvements in FACIT-F scores were also observed at week 14 in Group 2 (golimumab 50 mg + MTX) when compared with Group 1 (from placebo + MTX to golimumab 50 mg + MTX) (2.6 vs -2.4; p<0.001). FACIT-F positively changed as compared to placebo at 14 and 24 weeks (p<0.001).
Safety results	Through week 56, half of all patients who received ≥1 golimumab injection reported ≥1 AE. No unexpected safety events occurred.
Main results	ACR20 response at week 14 was significantly higher in Group 2 (40.9% [54/132]) compared with Group 1 (15.9% [21/132]; p<0.001). Greater proportions of patients in Group 2 compared with Group 1 had a DAS28- CRP response at week 14 (65.2% vs 30.3%, p<0.001) or ACR20 response at week 24 (42.4% vs 15.9%, p<0.001), and Group 2 had a significantly greater change in HAQ-DI at week 24 (0.26 vs 0.15, p<0.001). After week 24, the proportion of patients achieving ACR20 in Group 1 approached that in Group 2. Through week 16, 23.5% of Group 1 and 26.7% of Group 2 patients reported AEs. Among golimumab + MTX-treated patients, 50.2% and 4.2% had ≥ 1 AE or serious AE, respectively, through week 56. No unexpected safety signals were observed.
Follow-up	56 weeks
Conclusions	Among MTX-experienced Chinese patients with active RA, a significantly greater proportion of patients receiving golimumab + MTX had improvements in the signs and symptoms of RA compared with MTX monotherapy. Safety findings were consistent with previous studies of golimumab in patients with RA.

Li et al., 2018	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=216) ≈ Female 85% ≈ Age 48 years ≈ Disease duration differed groups between 6.6 and 9.5 years According to the American College of Rheumatology (ACR) 1987 revised criteria
Intervention(s)	Tofacitinib + conventional synthetic disease-modifying anti rheumatic drugs (csDMARDs)
Intervention(s) characteristics	Data were analyzed from a sub-population of Chinese patients with RA enrolled in the randomized, 12-month, double-blind, placebo-controlled, parallel group, Phase 3 study, ORAL Sync (A3921046 [NCT00856544]). In ORAL Sync, patients with an inadequate response to treatment with one or more csDMARDs or biologic DMARDs (bDMARDs) at a stable dose were randomized 4 : 4 : 1 : 1 to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo switched to tofacitinib 5 mg twice daily (from placebo to tofacitinib 5 mg twice daily), or placebo switched to tofacitinib 10 mg twice daily (from placebo to tofacitinib 10 mg twice daily), respectively, all in combination with csDMARDs.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	There were no significant differences between the tofacitinib (5 mg twice daily: 3.3; 10 mg twice daily: 3.6) and placebo (1.5) groups in change from baseline in FACIT-F scores at 3 months. At 6 months, patients receiving tofacitinib 10 mg twice daily demonstrated statistically significant improvement in FACIT-F scores compared with placebo (4.0 vs. 0.6; $P < 0.05$). Improvements in FACIT-F scores were maintained in the tofacitinib groups between 6 and 12 months.
Safety results	Not mentioned
Main results	Overall, 216 patients were included (tofacitinib 5 mg twice daily, n = 86; tofacitinib 10 mg twice daily, n = 86; from placebo to tofacitinib 5 mg twice daily, n = 22; from placebo to tofacitinib 10 mg twice daily, n = 22). At month 3, tofacitinib elicited significant improvements in HAQ-DI, Pain, PtGA, PGA and SF-36 Physical Component Summary scores. Improvements were generally maintained through 12 months.
Follow-up	12 months
Conclusions	Tofacitinib 5 and 10 mg twice daily + csDMARDs resulted in improvements in health-related quality of life, physical function and Pain through 12 months in Chinese patients with RA.

Li et al., 2020	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=290) ≈ Female 80.3% ≈ Age 49.2 years ≈ Disease duration 9.9 years Defined by the ACR/EULAR 2010 Classification Criteria
Intervention(s)	Baricitinib 4-mg once daily
Intervention(s) characteristics	Most patients (approximately 80%) were from China. More patients achieved ACR20 response at week 12 with baricitinib than with placebo (58.6% vs 28.3%; p<0.001). Statistically significant improvements were also seen in HAQ-DI, DAS28-hsCRP, morning joint stiffness, worst tiredness, and worst joint pain in the baricitinib group compared to placebo at week 12. Through week 24, rates of treatment-emergent adverse events, including infections, were higher for baricitinib compared to placebo, while serious adverse event rates were similar between baricitinib and placebo.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Tiredness by severity numeric rating scale [NRS] 0-10 Fatigue was a secondary outcome
Effectiveness results	Significant improvements were observed in worst tiredness at week 12 for baricitinib compared to placebo (p≤0.001 for both comparisons).
Safety results	The rates of discontinuation resulting from AEs from baseline through week 24 were 2.1% with placebo and 1.4% with baricitinib and rates of serious AEs (SAEs) were the same (2.8%) in both groups. Although infections occurred more frequently with baricitinib compared to placebo (42.1% vs. 28.3%), few serious infections were reported in either group. There was no increase in neutropenia or lymphopenia and no imbalance in the number of patients with protocol-defined thrombocytosis (>600,000 cells/mm^3) between the baricitinib and placebo groups.
Main results	Most patients (approximately 80%) were from China. More patients achieved ACR20 response at week 12 with baricitinib than with placebo (58.6% vs. 28.3%; p<0.001). Statistically significant improvements were also seen in HAQ-DI, DAS28-hsCRP, morning joint stiffness, worst tiredness, and worst joint pain in the baricitinib group compared to placebo at week 12. Through week 24, rates of treatment-emergent adverse events, including infections, were higher for baricitinib compared to placebo, while serious adverse event rates were similar between baricitinib and placebo.
Follow-up	52 weeks
Conclusions	In patients with RA who had an inadequate response to MTX, baricitinib was associated with significant clinical improvements as compared with placebo

Li et al., 2021	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=231) ≈ Female, %: Baricitinib group: 89.7, Placebo group: 74.8 ≈ Age, years: Baricitinib group: 48.6, Placebo group: 47.7 ≈ Disease duration, years: Baricitinib group: 10.2, Placebo group: 9.2
Intervention(s)	Baricitinib
Intervention(s) characteristics	patients enrolled in RA-BALANCE were randomized 1:1 to receive orally baricitinib 4 mg once daily or placebo for 24 weeks (24- week, double-blind, placebo-controlled period) and patients receiving placebo were switched to baricitinib from the end of week 24 though week 52 (28-week, open-label period). Rescue treatment (open label baricitinib 4 mg) was available from week 16 at the discretion of the investigator.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	From week 4 (the first measure point after baseline), statistically significant (p≤0.05) improvements in FACIT-F were observed in the baricitinib-treated group compared with placebo. Significant improvements in efficacy measures were sustained through 24 weeks.
Safety results	Not stated
Main results	Statistically significant (p≤0.05) improvements were observed as early as week 1 or 2 for the baricitinib group compared to placebo in almost all main efficacy measures. For other outcomes including 66 swollen joint count, 68 tender joint count, FACIT-F, and DAS28-hsCRP≤3.2 response rate, differences were evident (p≤0.05) by week 4 in the baricitinib group compared with placebo. Significant improvements in all efficacy measures were sustained through 24 weeks.
Follow-up	24 weeks
Conclusions	Baricitinib demonstrated a rapid onset of efficacy on ACR20 response, ACR core set values, disease activity, and patient-reported outcome improvements in Chinese patients from RA-BALANCE.

Liu et al., 2019	
Participants characteristics (number, age, disease criteria, details)	Primary Sjögren's syndrome (pSS) patients (n=314) ≈ Female, %: TGP group: 97.2, Placebo group: 93.2 ≈ Age, years: TGP group: 48.9, Placebo group: 47.5 ≈ Disease duration, years: Baricitinib group: 36, Placebo group: 36.1 Classified according to the 2002 American-European Consensus Group Criteria
Intervention(s)	Total glucosides of peony (TGP)
Intervention(s) characteristics	The TGP capsule was 0.3 g and contained glucosides of peony no less than 104 mg. The capsule was provided by Ningbo Lansen Pharmaceutical Co. Ltd. Ningbo, China. The dose was two capsules twice or three times a day. As the efficacy might be associated with dose to a certain degree, and the incidence of adverse effects was also likely to correlate to the dose (including soft stools and increased number of defecation), the dose was designed as two capsules twice a day for the first week, and increased to two capsules three times a day, which was in accordance with the manufacturer's instructions. Patients were randomly assigned to be treated either with oral TGP, in the TGP group, or with placebo, in the placebo group, in a 2:1 ratio.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue - VAS Fatigue was a secondary outcome
Effectiveness results	Fatigue VAS of the TGP group were significantly improved compared with those of the placebo group at weeks 24 ($p<0.001$).
Safety results	There were 23 patients (10.9%) who reported adverse events in the TGP group, and 3 patients (2.9%) reported adverse events in the placebo group. In the TGP group, the adverse events reported by 12 patients were related to the TGP treatment. Adverse reactions to TGP included gastrointestinal discomfort and diarrhea. Among these 12 patients, two patients discontinued TGP use due to intolerance. In addition, 10 patients discontinued TGP use due to other adverse reactions unrelated to TGP treatment. No severe adverse events were observed during the study.
Main results	Dry eyes/throat/vagina VAS, fatigue VAS, mental discomfort VAS, PGA, Schirmer's test, and ESR also improved more in the TGP group than in the placebo group (all $p<0.05$). Stimulated salivary flow-rate values increased in the TGP group at week 12 but not at week 24. Adverse events in TGP group were 10.9%.
Follow-up	24 weeks
Conclusions	TGP can alleviate some dryness symptoms as well as disease activity in pSS patients over 24 weeks. TGP was well tolerated by study subjects. TGP seems to be an effective and safe treatment for pSS.

Mariette et al., 2004	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren's syndrome (SS) patients (n=103) ≈ Female, %: not stated ≈ Age, years: Infliximab group: 54.4, Placebo group: 53.8 ≈ Disease duration, years: Infliximab group: 4, Placebo group: 4.9 Patients fulfilled the new American-European Consensus Group criteria for SS
Intervention(s)	Infliximab
Intervention(s) characteristics	Patients with primary SS were randomly assigned to receive infliximab infusions (5 mg/kg) or placebo at weeks 0, 2, and 6 and were followed up for 22 weeks.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue - VAS Fatigue was a secondary outcome
Effectiveness results	2 groups did not differ in their scores on fatigue- VAS during the study. 30% decrease in fatigue VAS at week-10 (change from baseline) was 31.5% in infliximab group and 30.6% in placebo group (p=0.92). In addition, 30% decrease in fatigue VAS at week-22 (change from baseline) was 24.1% in infliximab group and 24.5% in placebo group (p=0.96).
Safety results	Seven patients experienced severe adverse events. Six of the adverse events occurred in the infliximab group (2 were infusion reactions, 1 an isolated cutaneous facial eruption without any anti-DNA antibodies, 1 autoimmune hepatitis, 1 pneumococcal septicemia, and 1 breast cancer) and 1 occurred in the placebo group (polyclonal lymph node enlargement).
Main results	At week 10, 26.5% of patients receiving placebo and 27.8% of patients treated with infliximab had a favorable overall response (p=0.89), and at week 22, 20.4% of the placebo group and 16.7% of the infliximab group had a favorable response (p=0.62). In addition, the 2 groups did not differ in any of the secondary end points over the 22 weeks of the trial. Severe adverse events reported in the infliximab group did not differ from those observed in previous studies.
Follow-up	22 weeks
Conclusions	This randomized, double-blind, placebo-controlled study of an anti-TNF agent did not show any evidence of efficacy of infliximab in primary SS.

Marzo-Ortega et al., 2017	
Participants characteristics (number, age, disease criteria, details)	AS patients (n=219) ≈ Female 30.1% ≈ Age 43.3 years ≈ Disease duration 6.2 years Fulfilling the Modified New York Criteria
Intervention(s)	Secukinumab
Intervention(s) characteristics	Patients with active AS were randomized to subcutaneous secukinumab 150 mg, 75 mg, or placebo at baseline; weeks 1, 2, and 3; and every 4 weeks from week 4.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Improvements were sustained in FACIT-fatigue scores through 104 weeks of secukinumab treatment. Least squares mean change at 16 weeks was 8.1, 6.7, and 3.3 in secukinumab 150 mg group, secukinumab 75 mg group, and placebo group, respectively. Additionally, least squares mean change at 104 weeks was 11.2 and 9.8 in secukinumab 150 mg group and secukinumab 75 mg group, respectively.
Safety results	Most of the AEs were mild to moderate in severity. The most frequent treatment-emergent AEs with secukinumab were nasopharyngitis, upper respiratory tract infection, diarrhea, headache, and hypertension. The rate of treatment-emergent serious infections and infestations was low among all patients exposed to secukinumab (i.e., originally randomized patients to secukinumab and those who switched from placebo) over the entire safety-reporting period. No patient discontinued treatment because of a serious infection. There was a single case of malignant melanoma in a patient receiving the secukinumab 150 mg dose, which led to interruption of the study treatment. Three cases of Crohn's disease (2 patients with 75 mg [leading to study discontinuation] and 1 patient with 150 mg) were reported, which were considered SAEs.
Main results	Of 219 randomized patients, 60 of 72 (83.3%) and 57 of 73 (78.1%) patients completed 104 weeks of treatment with secukinumab 150 mg and 75 mg, respectively; ASAS20/ASAS40 response rates at week 104 were 71.5% and 47.5% with both secukinumab doses, respectively. Clinical improvements with secukinumab were sustained through week 104 across all secondary end points. Across the entire treatment period (mean secukinumab exposure 735.6 days), exposure-adjusted incidence rates for serious infections and infestations, Crohn's disease, malignant or unspecified tumours, and major adverse cardiac events with secukinumab were 1.2, 0.7, 0.5, and 0.7 per 100 patient-years, respectively. No cases of tuberculosis reactivation, opportunistic infections, or suicidal ideation were reported.
Follow-up	104 weeks
Conclusions	Secukinumab provided sustained improvement through 2 years in the signs and symptoms of AS, with a safety profile consistent with previous reports.

Mease et al., 2008	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=367) ≈ Female 80% ≈ Age 51 years ≈ Disease duration 11 years According to the revised ACR 1987 criteria
Intervention(s)	Rituximab 500 mg or 1000 mg
Intervention(s) characteristics	Eligible patients were randomized to receive placebo, 2 × 500mg rituximab, or 2 × 1000mg rituximab as intravenous infusions administered on days 1 and 15. Additionally, patients were concurrently randomized to receive one of 3 doses of glucocorticoids. Concomitant MTX therapy of 10 to 25 mg/week (oral or parenteral) was required in all treatment groups. Patients were followed for 24 weeks, and from Week 16 to Week 24, patients who demonstrated <20% improvement from screening in SJC and TJC were eligible to enter a rescue arm to receive open-label, active treatment. Outcome measures included ACR response criteria, Disease Activity Score in 28 joints (DAS28), SF-36, FACIT-Fatigue, and HAQ.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	Both the rituximab 500 mg and 1000 mg treatment groups had significantly different mean scores on the FACIT-Fatigue compared with the placebo group (p=0.009 and p<0.001, respectively). In addition, there was a significant treatment-by-visit interaction for both the rituximab 500mg and 1000mg groups (both, p<0.001) compared with the placebo group. Both the rituximab 500mg and 1000mg groups reported improvements in FACIT-Fatigue scores over 12 weeks followed by maintenance of these effects over the remaining 12 weeks of the study. Significant differences between the rituximab groups and placebo were observed at 12 weeks, and the difference persisted over the course of the clinical trial (all p<0.05). The observed change over 24 months was 7.63 points for the rituximab 500 mg group and 8.20 points for the rituximab 1000 mg group, compared with 3.91 points in the placebo group. The placebo and rituximab-treated groups were compared to see if those receiving rituximab treatment were more likely to exceed the MCID of 3.5 points on the FACIT-Fatigue. There were significant differences between placebo (35.2%) and rituximab 500 mg (55.3%), and between placebo and rituximab 1000 mg (65.6%) on the MCID of the FACIT-Fatigue (p<0.05).
Safety results	Rituximab was well tolerated; the type and severity of infections was similar to those for placebo.
Main results	At 24 weeks, the rituximab 500 mg and 1000 mg groups both reported statistically significantly greater improvements on the SF-36 physical component summary (4.37 and 4.89 points higher, respectively, vs placebo; p<0.001). SF-36 physical function, bodily pain, vitality, social function, and role physical subscale scores also statistically significantly improved vs placebo. At 24 weeks, 62.6% and 67.2% of the rituximab 500 mg and 1000 mg groups, respectively, exceeded the MCID of 0.22 in HAQ (p<0.001). For FACIT-Fatigue, 55.3% and 65.6% of patients exceeded the MCID of 3.5 points compared with 35.2% of placebo over 24 weeks (p<0.001). ACR20/50/70 and EULAR responders demonstrated greater improvements in mean baseline to 24-week changes in SF-36 and FACIT-Fatigue scores compared with non-responders (p<0.05).
Follow-up	24 weeks
Conclusions	Both rituximab doses in combination with methotrexate were effective in improving all HRQOL outcomes in patients with active RA consistent with clinical efficacy.

Meijer et al., 2010	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren's syndrome (SS) patients (n=30) ≈ Female 97% ≈ Age, years: Rituximab group: 43, Placebo group: 43 ≈ Disease duration, months: Rituximab group: 63, Placebo group: 67 According to the revised American-European Consensus Group criteria
Intervention(s)	Rituximab 1,000 mg
Intervention(s) characteristics	Patients were treated with either rituximab (1,000 mg) or placebo infusions on days 1 and 15. Patients were assigned randomly to a treatment group in a ratio of 2:1 (rituximab:placebo). Follow-up was conducted at 5, 12, 24, 36, and 48 weeks.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Multidimensional Fatigue Inventory (MFI) Fatigue was a secondary outcome
Effectiveness results	The MFI scores showed the strongest improvements in the rituximab group. Compared with that in the placebo group, patients receiving rituximab showed a significant change in the MFI score, showing decreased scores for reduced activity from baseline to week 36 (p=0.023) and for reduced motivation from baseline to week 12 (p=0.039).
Safety results	One female patient with diabetes developed a mild serum sickness-like disease, which was identified 14 days after the first infusion of rituximab. None of the 6 patients who had discontinued immunosuppressive drugs 1-6 months prior to rituximab treatment developed serum sickness-like disease. None of the infections required hospitalization. No opportunistic infections were observed.
Main results	In the rituximab group, significant improvements, in terms of the mean change from baseline compared with that in the placebo group, were found for the primary end point of the stimulated whole saliva flow rate (p=0.038 vs placebo) and also for various laboratory parameters (B cell and rheumatoid factor [RF] levels), subjective parameters (Multidimensional Fatigue Inventory [MFI] scores and visual analog scale [VAS] scores for sicca symptoms), and extraglandular manifestations. Moreover, in comparison with baseline values, rituximab treatment significantly improved the stimulated whole saliva flow rate (p=0.004) and several other variables (e.g., B cell and RF levels, unstimulated whole saliva flow rate, lacrimal gland function on the lissamine green test, MFI scores, Short Form 36 health survey scores, and VAS scores for sicca symptoms). One patient in the rituximab group developed mild serum sickness-like disease.
Follow-up	48 weeks
Conclusions	These results indicate that rituximab is an effective and safe treatment strategy for patients with primary SS.

Merrill et al., 2010	
Participants characteristics (number, age, disease criteria, details)	SLE patients (n=175) ≈ Female 90.9% ≈ Age 38.6 years ≈ Disease duration 7 years American College of Rheumatology [ACR] criteria for the classification of SLE
Intervention(s)	Abatacept
Intervention(s) characteristics	SLE patients with polyarthritis, discoid lesions, or pleuritis and/or pericarditis were randomized at a ratio of 2:1 to receive abatacept (≈10 mg/kg of body weight) or placebo. Prednisone (30 mg/day or equivalent) was given for 1 month, and then the dosage was tapered.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue - VAS Fatigue was a secondary outcome
Effectiveness results	The adjusted mean change in the fatigue score from baseline to 12 months in the abatacept and placebo groups, respectively, was -20.27 and -10.82). Improvements in the fatigue scores that were observed in the abatacept treated patients exceeded the minimum clinically important difference. For fatigue, improvements in the placebo group also exceeded this threshold.
Safety results	Over 12 months, the percentage of patients with any AEs was comparable between treatment groups, with 90.9% in the abatacept group and 91.5% in the placebo group reporting an AE. The most frequently reported AEs (10% patients in either group) were upper respiratory tract infection (25 [20.7%] receiving abatacept vs 9 [15.3%] receiving placebo), headache (25 [20.7%] vs 10 [16.9%]), back pain (15 [12.4%] vs 5 [8.5%]), diarrhea (14 [11.6%] vs 4 [6.8%]), nasopharyngitis (3 [2.5%] vs 7 [11.9%]), and urinary tract infection (13 [10.7%] vs 5 [8.5%]). The proportion of patients with SAEs was higher in the abatacept group than in the placebo group (24 [19.8%] and 4 [6.8%] patients, respectively). Serious infections were reported in 3 abatacept treated patients and 1 placebo-treated patient.
Main results	The proportion of new BILAG A/B flares over 12 months was 79.7% (95% CI=72.4 to 86.9) in the abatacept group and 82.5% (95% CI=72.6 to 92.3) in the placebo group (treatment difference -3.5; 95% CI=-15.3 to 8.3). Other prespecified flare end points were not met. In post hoc analyses, the proportions of abatacept treated and placebo-treated patients with a BILAG A flare were 40.7% (95% CI=31.8 to 49.5) vs 54.4% (95% CI=41.5 to 67.3), and the proportions with physician assessed flare were 63.6% (95% CI=54.9 to 72.2) and 82.5% (95% CI=72.6 to 92.3), respectively; treatment differences were greatest in the polyarthritis group. Prespecified exploratory patient-reported outcomes (Short Form 36 health survey, sleep problems, fatigue) demonstrated a treatment effect with abatacept. The frequency of adverse events (AEs) was comparable in the abatacept and placebo groups (90.9% vs 91.5%), but serious AEs (SAEs) were higher in the abatacept group (19.8 vs 6.8%). Most SAEs were single, disease-related events occurring during the first 6 months of the study (including the steroid taper period).
Follow-up	12 months
Conclusions	Although the primary/secondary end points were not met in this study, improvements in certain exploratory measures suggest some abatacept efficacy in patients with non–life-threatening manifestations of SLE. The increased rate of SAEs requires further assessment.

Merrill et al., 2016	
Participants characteristics (number, age, disease criteria, details)	SLE patients (n=1124) ≈ Female, %: Tabalumab 120 Q2W group: 91.9, Tabalumab 120 Q4W group: 92, Placebo group: 92.8 ≈ Age, years: Tabalumab 120 Q2W group: 42, Tabalumab 120 Q4W group: 41, Placebo group: 42 ≈ Disease duration 8 years Fulfilled 4/11 American College of Rheumatology criteria
Intervention(s)	Tabalumab
Intervention(s) characteristics	Tabalumab is a human IgG4 monoclonal antibody that neutralises membrane and soluble B-cell activating factor (BAFF). Patients received standard of care plus subcutaneous study drug, starting with a loading dose (240mg) at week 0 and followed by 120 mg every 2 weeks (120 Q2W), 120mg every 4 weeks (120 Q4W) or placebo.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Brief Fatigue Index (BFI) Fatigue was a secondary outcome
Effectiveness results	The change from baseline in BFI) were not significantly different when comparing tabalumab and placebo. Least square mean change from baseline in BFI was −0.78 (p=0.957) in 120 Q2W group, −0.70 (p=0.779) in 120 Q4W group, and −0.76 in placebo group.
Safety results	There were no differences in the number of deaths, the frequency of SAEs or TEAEs or the number of patients who discontinued due to an AE between groups. The majority of TEAEs were mild to moderate in severity.
Main results	Clinical characteristics were balanced across groups. The primary endpoint was met with 120 Q2W (38.4% vs 27.7%, placebo; p=0.002), but not with the less frequent 120 Q4W regimen (34.8%, p=0.051). Although key secondary endpoints (time to severe flare, corticosteroid sparing and fatigue) were not met, patients treated with tabalumab had greater SRI-5 response rates in a serologically active subset and improvements in more stringent SRI cut-offs, SELENASLEDAI, Physician's Global Assessment, anti-double stranded DNA antibodies, complement, total B cells and immunoglobulins. The incidences of deaths, serious adverse events (AEs), and treatment-emergent AEs were similar in the 120 Q2W, 120 Q4W and placebo groups, but depression and suicidal ideation, albeit rare events, were more commonly reported with tabalumab.
Follow-up	52 weeks
Conclusions	SRI-5 was met with 120 Q2W and although key secondary endpoints were not met, numerous other secondary endpoints significantly improved in addition to pharmacodynamic evidence of BAFF pathway blockade. The safety profile for tabalumab was similar to placebo, except for depression and suicidality, which were uncommon.

Mittendorf et al., 2007	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=505) ≈ Female 77.2 % ≈ Age 55 years ≈ Disease duration 12.4 years Defined by the 1987 revised ACR criteria
Intervention(s)	Adalimumab
Intervention(s) characteristics	This long-term, open-label, health outcomes extension study (DE033) included 505 patients with longstanding RA who had received adalimumab therapy during 1 of 6 Phase I-III studies, of which DE026 included a double-blind, randomized, placebo-controlled period of at least 12 weeks in duration (Figure 1). After that, patients received adalimumab 40 mg every other week and were followed for up to 144 weeks. Patients receiving placebo in the preceding DE026 trial were switched to adalimumab treatment at the beginning of this open-label study.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	In the DE026 subgroup, rapid and statistically significant improvements from baseline in FACIT-F scores were observed after 12 weeks of adalimumab treatment and were maintained for more than 3 years. The FACIT-F score for adalimumab patients at baseline was 26.08±10.41 and increased to 34.63±11.67 at Week 26. From Week 26 to Week 170, FACIT-F scores remained stable (33.28±11.42 at Week 170); this small change over time was not clinically meaningful. The difference between adalimumab and placebo and the differences in change from baseline between placebo and adalimumab treatments were both statistically significant and clinically meaningful at each timepoint assessed. For adalimumab-treated patients, mean improvements in FACIT-Fatigue scores were more than 4, indicating clinically meaningful improvements. The changes from baseline in fatigue scores for the placebo group were not statistically significant or clinically important.
Safety results	Not stated
Main results	All assessed measures (FACIT-F, HUI3, SF-36) showed a rapid and statistically significant improvement from baseline following initiation of adalimumab therapy. This effect was maintained over the study period for a mean of 1.6 years in all applied measures. HRQOL data from all tested instruments were significantly correlated with each other
Follow-up	3 years
Conclusions	Chronic therapy with adalimumab improved measures of fatigue and HRQOL in patients with longstanding RA.

Moreland et al., 2006	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=435) ≈ Female, %: Recent-onset RA group: Methotrexate subgroup: 76, Etanercept subgroup: 73; Established RA group: Placebo subgroup: 77, Etanercept subgroup: 72 ≈ Age, years: Recent-onset RA group: Methotrexate subgroup: 48, Etanercept subgroup: 50; Established RA group: Placebo subgroup: 50, Etanercept subgroup: 53 ≈ Disease duration: Recent-onset RA group: Methotrexate subgroup: 11 months, Etanercept subgroup: 11 months; Established RA group: Placebo subgroup: 12 years, Etanercept subgroup: 12 years
Intervention(s)	Etanercept in recent-onset (mean duration 11 months) or established (mean duration 12 years) RA
Intervention(s) characteristics	Patients participating in either of 2 multicenter, randomized, double-blind clinical trials were included. In one trial, patients with recent-onset RA received either etanercept 25 mg twice weekly or methotrexate in a double-blind fashion for 12 months, then open label for 12 months. All patients then received open-label etanercept. In the second trial, patients with established RA received etanercept 25 mg or placebo twice weekly for 6 months in a double-blinded fashion, then open-label etanercept
Control	Recent-onset or established RA
Outcomes of interest (types and measuring instruments)	Health Assessment Questionnaire (HAQ) fatigue domain Fatigue was a primary outcome
Effectiveness results	In the trial of patients with recent-onset RA, the reduction of fatigue was more rapid in the etanercept group compared with the methotrexate group. A significant difference in fatigue was observed at weeks 2, 4, and 8. For the remainder of the study, patients in the etanercept group consistently reported a greater reduction in fatigue of 23-29% compared with the 17-24% reduction in patients who started on methotrexate. Although the difference between the groups did not reach statistical significance beyond month 2 (except at month 24), reduction in fatigue was sustained throughout the entire 44 months of follow-up. Patients in both groups showed a significant reduction in fatigue relative to baseline at all time points ($p<0.0001$). In the trial of patients with established RA, the etanercept group had a significantly greater reduction in fatigue from baseline compared with the placebo group in the double-blind phase of the trial, as expected. Patients originally in the placebo group showed an immediate reduction in HAQ fatigue scores after being switched to etanercept at month 6. Despite this, patients who initially received placebo had a consistently smaller percent reduction in fatigue score compared with patients who initially received etanercept during the open-label phase, although this difference was not statistically significant. After at least 4 weeks of etanercept treatment, mean reduction in fatigue score was 25-36% in patients who initially received etanercept and 20 –27% in patients who initially received placebo. Similar to the trend observed in the patients with recent-onset RA, the effect of etanercept on fatigue reduction in patients with established RA was sustained throughout 46 months of follow-up.
Safety results	Not stated
Main results	Patients with recent-onset RA who received etanercept had a significantly faster improvement in fatigue than those receiving methotrexate in the first 2 months. Subsequently, patients receiving etanercept and methotrexate had 23-29% and 17-24% reductions in fatigue scores, respectively. In the group with established RA, patients who received etanercept had significantly greater reductions in fatigue than those receiving placebo during the blinded period. Patients initially receiving etanercept sustained a mean fatigue reduction of 25-36% for the entire follow-up. Patients achieving clinically meaningful improvement in fatigue were more likely to meet the American College of Rheumatology improvement criteria.
Follow-up	46 weeks
Conclusions	Etanercept therapy reduces fatigue in patients with recent-onset or established RA. Improvement in fatigue was sustained for up to 46 months and correlated with other RA-relevant outcomes.

Norheim et al., 2012	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren's syndrome (pSS) patients (n=26) ≈ Female, %: Anakinra group: 69, Placebo group: 77 ≈ Age, years: Anakinra group: 55, Placebo group: 54 ≈ Disease duration, years: Anakinra group: 5, Placebo group: 8 Defined by the 2002 American-European Consensus Group criteria for pSS
Intervention(s)	Anakinra
Intervention(s) characteristics	Patients were randomly assigned to receive double-blinded therapy with anakinra (KineretTM, BioVitrum AB, SE-112 76 Stockholm, Sweden) 100 mg/day or a placebo (0.9% NaCl in identical syringes) for four weeks. Anakinra or the placebo was injected subcutaneously over 30 seconds in the abdominal or thigh region. The assigned treatment was withheld when infection or fever was present. The first injection was given at week 0 and the last at week 4
Control	Placebo
Outcomes of interest (types and measuring instruments)	Visual analogue scale (VAS) – fatigue, Fatigue Severity Scale (FSS) Fatigue was a primary outcome
Effectiveness results	There was no significant difference between the groups in fatigue score at week 4 when adjusting for baseline values, p=0.1. There was a highly significant improvement in fatigue at week 4, compared to baseline, in the group on the active drug (p=0.005), and an almost significant improvement in the placebo treated group, p=0.053. The mean improvement in fatigue VAS at week 4 was 37% (SE 10.2%) in the active drug group and 13.5% (SE 8.0%) in the placebo group. Six out of 12 patients (50%) on the active drug and one out of 13 patients on placebo reported 50% reduction in fatigue VAS score from baseline to week 4, p=0.03. There were no significant changes in FSS scores in either treatment group during the study. Fatigue levels returned to baseline one week after the last injection in both groups (week 5).
Safety results	Two serious adverse events (SAE) were observed in each group. One patient on anakinra developed a severe injection site reaction and stopped medication on day 8. Three patients, two on the active drug and one on placebo, had a transient episode of neutropenia. White blood cell count normalised spontaneously during continued treatment according to the protocol. Injection site reactions were common and occurred in seven of the 13 patients on the active drug (54%), and in two on placebo (15%). Apart from the one reported as a SAE, injection site reactions were transient and mild, with a burning sensation as the main symptom in the placebo group.
Main results	There was no significant difference between the groups in fatigue scores at week 4 compared to baseline after treatment with anakinra. However, six out of 12 patients on anakinra vs one out of 13 patients on the placebo reported a 50% reduction in fatigue VAS (p=0.03). There were two serious adverse events in each group.
Follow-up	4 weeks
Conclusions	This randomised, double-blind, placebo-controlled trial of IL-1 blockade did not find a significant reduction in fatigue in pSS in its primary endpoint. A 50% reduction in fatigue was analysed post-hoc, and significantly more patients on the active drug than on placebo reached this endpoint. Although not supported by the primary endpoint, this may indicate that IL-1 inhibition influences fatigue in patients with pSS.

Petri et al., 2017	
Participants characteristics (number, age, disease criteria, details)	SLE patients (n=547) Female, %: Blisibimod pooled group: 92.4, Placebo group: 95.5 ≈ Age, years: Blisibimod pooled group: 37.1, Placebo group: 37.9 ≈ Disease duration, years: Blisibimod pooled group: 5.7, Placebo group: 6.5 Fulfilling the American College of Rheumatology (ACR) classification criteria for SLE
Intervention(s)	Blisibimod
Intervention(s) characteristics	Blisibimod (A-623, AMG 623) is a potent and selective inhibitor of B-cell activating factor (BAFF). were randomized 1:1:1:1:1:1 to receive subcutaneous blisibimod in one of three dose levels (100 mg weekly (QW), 200 mg QW, or 200 mg every four weeks (Q4W)), or corresponding volume-matched and frequency-matched placebo. Randomization was stratified by baseline SELENA-SLEDAI score (6–9 vs 10) and race (African descent or indigenous American vs other).
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Despite diminishing participant numbers after Week 24, improvements in patient self-reported fatigue were observed in the change in FACIT-Fatigue score from baseline through Week 52 in individuals randomized to both placebo and blisibimod. However, these improvements were more profound among patients randomized to the two higher doses of blisibimod (100mg QW and 200mg QW), and especially at the highest dose of 200mg QW blisibimod. The minimal clinically important difference for SLE of 5.96 was achieved among individuals randomized to the 200mg QW blisibimod arm from Week 8 through Week 52. When compared with placebo, the effects of blisibimod (100mg QW or 200 mg QW) on fatigue were statistically significant ($p<0.05$) at several time points from Weeks 8 through Week 28. However, statistical evaluation of drug effect after Week 28 is confounded by the rapid decline in evaluable patients.
Safety results	Blisibimod was safe and well tolerated at all dose levels with no meaningful imbalances in serious adverse events or infections between blisibimod and placebo.
Main results	Statistically significant improvements in FACIT-Fatigue score were observed among individuals randomized to blisibimod, especially in the 200 mg QW group where favorable effects on disease activity with blisibimod compared to placebo were observed as early as Week 8. The mean improvement from baseline of 6.9 points at Week 24, compared with 4.4 points with placebo, met the criteria for minimal clinically important improvement difference defined for patients with SLE. Despite concomitant improvements in FACIT-Fatigue, SLE Responder Index (SRI) and SLE biomarkers (reported previously), FACIT-Fatigue score correlated only weakly with disease activity.
Follow-up	24 weeks
Conclusions	While poor correlation between fatigue and disease activity is not new, the observation that correlation remains poor despite concurrent population improvements in disease and fatigue brings a new facet to our understanding of SLE.

Pincus et al., 2009	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=31) Female, %: Prednisone group: 66.7, Placebo group: 62.5 ≈ Age, years: Prednisone group: 53.3, Placebo group: 50.1 ≈ Disease duration, years: Prednisone group: 8.1, Placebo group: 4.4
Intervention(s)	1–4 mg prednisone
Intervention(s) characteristics	Patients were taking stable doses of 1-4 mg prednisone with stable clinical status, documented quantitatively by patient questionnaire scores. The protocol included three phases: (1) equivalence: 1-4 study prednisone 1 mg tablets taken for 12 weeks to ascertain their efficacy compared with the patient's usual tablets before randomisation; (2) transfer: substitution of a 1 mg prednisone or identical placebo tablet every 4 weeks (over 0-12 weeks) to the same number as baseline prednisone; (3) comparison: observation over 24 subsequent weeks taking the same number of either placebo or prednisone tablets as at baseline.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue – VAS Fatigue was a secondary outcome
Effectiveness results	Participants in the placebo group had higher median changes (indicating poorer status) with worsening scores for fatigue (in placebo group: 0.45, in prednisone group:0).
Safety results	No meaningful toxicities were reported by the participants in either group, as anticipated, since all participants had been taking stable doses of 1–4 mg/day prednisone before the trial, many for long periods. No significant changes in weight or blood pressure were seen within either group or between groups.
Main results	In ''intent-to-treat'' analyses, 3/15 prednisone and 11/16 placebo participants withdrew (p=0.03). Among participants eligible for the primary outcome, 3/13 prednisone and 11/15 placebo participants withdrew for lack of efficacy (p=0.02). No meaningful adverse events were reported, as anticipated.
Follow-up	24 weeks
Conclusions	Efficacy of 1–4 mg prednisone was documented. Evidence of statistically significant differences with only 31 patients may suggest a robust treatment effect.

Pope et al., 2015	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=1063) Female 78% ≈ Age 55 years ≈ Disease duration 8.7 years Defined by the 1987 ACR criteria
Intervention(s)	Certolizumab pegol (CZP)
Intervention(s) characteristics	Patients were stratified by baseline MTX use, prior anti-TNF use, and disease duration (<2 years vs. ≥2 years) and randomized 4:1 to receive, in addition to their existing treatment, either (1) a CZP 400-mg loading dose at weeks 0, 2, and 4, followed by CZP 200 mg every 2 weeks; or (2) placebo injection (control) every 2 weeks for the initial 12-week double-blind RCT. After completing the 12-week RCT, patients could enter the open-label phase and receive CZP 200 mg every 2 weeks (following the loading dose for patients originally randomized to placebo).
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue – VAS Fatigue was a secondary outcome
Effectiveness results	Early and clinically meaningful improvements in PROs were observed. Improvements in fatigue were reported with CZP compared with placebo from week 2 (first time point assessed) through week 12. At week 12, compared with placebo patients, more CZP patients had improvements greater than or equal to the MCID for fatigue (56.4 % vs. 46.2 %; p=0.008). Differences between treatment arms for MCID improvement were seen by week 2 for fatigue (p<0.001). Rates of CZP patients reporting MCID were maintained up to week 28 (fatigue 64.4 %).
Safety results	Not stated
Main results	Early significant and clinically meaningful improvements in all PROs were observed to week 12 with CZP vs. placebo and were maintained to the end of the trial (week 28). At week 12, up to one-third more CZP patients showed improvements compared with placebo that were greater than or equal to the minimal clinically important difference (MCID) in fatigue, sleep problems, pain, PtGA, RADAI, and RAPID3. The changes in PROs were correlated with clinical measures of disease activity, including the Disease Activity Score in 28 joints using C-reactive protein as well as tender and swollen joint counts.
Follow-up	28 weeks
Conclusions	Rapid improvements in PROs were seen in patients with RA treated with CZP. The magnitude of improvement exceeded the MCID in multiple domains and demonstrated that CZP improves aspects of health-related quality of life that are meaningful to patients and superior to placebo. PROs provide information complementary to clinical outcomes in assessment of treatment benefits.

Posada et al., 2021	
Participants characteristics (number, age, disease criteria, details)	Primary Sjögren's syndrome (SS) patients (n=28) Female 100%: ≈ Age, years: RSLV-132 group: 56.5, Placebo group: 59.6 ≈ Disease duration, years: not stated Defined by the American–European Consensus Group 2002 classification criteria
Intervention(s)	RSLV-132 (an RNase Fc fusion protein)
Intervention(s) characteristics	Patients were randomized to receive treatment with RSLV-132 or placebo intravenously once per week for 2 weeks, and then every 2 weeks for 12 weeks. Eight patients received placebo and 20 patients received RSLV-132 at a dose of 10 mg/kg.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F), Profile of Fatigue (ProF) Fatigue was a primary outcome
Effectiveness results	The mean ESSPRI fatigue score was reduced in the RSLV-132 group at day 99 (mean change from baseline −1.4 points) whereas the mean change from baseline was 0 in the placebo group. Mean FACIT-F scores increased from baseline by a mean 1.13 points in the placebo group compared to a mean increase of 5.90 points in the RSLV-132 group. Subject-level data revealed that 25% of subjects in the placebo group and 45% of the RSLV-132–treated subjects achieved minimal clinically important improvement in the FACIT-F score by day 99. With respect to the mean change from baseline in the ProF mental fatigue score, the placebo group experienced a mean reduction of 0.02 points, while the RSLV-132–treated group experienced a mean reduction of 1.04 points. The ProF can be subdivided into somatic and mental components. The placebo group did not experience an improvement in the somatic fatigue score, whereas the RSLV-132 group had a mean decrease in the somatic fatigue score of 0.8 points. The largest change was observed in the mental fatigue component, in which the placebo group experienced a mean decrease in the mental fatigue score of 0.06 points, while the RSLV-132 group experienced a mean decrease in the mental fatigue score of 1.53 points.
Safety results	The incidence of treatment emergent adverse events, serious adverse events, and drug related adverse events were comparable between the RSLV-132 and placebo treatment groups. No deaths occurred during the study. There were no serious infections or infusion reactions observed in either treatment group during the study. No patients discontinued the study drug due to an adverse event. One patient in the RSLV-132 group experienced a serious adverse event and was hospitalized for parotitis 88 days after receiving the last dose of study drug.
Main results	Patients randomized to receive RSLV-132 experienced clinically meaningful improvements in the ESSPRI score (p=0.27), FACIT-F score (p=0.05), ProF score (p=0.07), and DSST (p=0.02) from baseline to day 99, whereas patients who received placebo showed no changes in any of these clinical efficacy measures. This improvement was significantly correlated with increased expression of selected interferon-inducible genes (Pearson's correlations, each $p<0.05$).
Follow-up	12 weeks
Conclusions	Administration of RSLV-132 improved severe fatigue, as determined by 4 independent patientreported measures of fatigue, in patients with primary SS.

Revicki et al., 2008	
Participants characteristics (number, age, disease criteria, details)	AS patients (n=315) ≈ Female 25.1% ≈ Age 42.2 years ≈ Disease duration 10.6 years According to the modified New York criteria
Intervention(s)	Adalimumab
Intervention(s) characteristics	The Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis (ATLAS) was an ongoing 5-year study that included an initial 24-week, randomized, placebo-controlled, double-blind period. Patients were randomized to adalimumab 40 mg or placebo by subcutaneous injection every other week.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue - SF-36 vitality domain and Bath AS Disease Activity Index (BASDAI) fatigue domain Fatigue was a primary outcome
Effectiveness results	After 2 weeks of treatment, adalimumab-treated patients reported significant improvement in fatigue compared with placebo-treated patients (BASDAI fatigue, -1.1 vs -0.3; p<0.001). By Week 12, fatigue scores improved by 2.2 points (95% CI=-2.5 to -1.8) in adalimumab-treated patients compared with 0.7 points (95% CI=-1.2 to -0.2) in placebo-treated patients. The reduction in fatigue as measured by BASDAI question 1 was maintained through Week 24 in the adalimumab group. Further, the mean change from baseline to Week 12 in SF-36 vitality scores improved more in the adalimumab group compared with the placebo group (12.9 vs 6.8; p<0.01), and this magnitude of improvement was maintained through Week 24 (14.5 vs 5.9; p<0.001).
Safety results	Adalimumab-treated patients reported more adverse events (75.0% vs 59.8% of placebo-treated patients; p<0.05), but there was no statistically significant difference in the incidence of infections. Most adverse events were mild or moderate in severity.
Main results	Of 315 patients enrolled, 208 received adalimumab 40 mg and 107 received placebo. At Week 12, adalimumab-treated patients experienced significant improvement compared with placebo-treated patients in the SF-36 bodily pain score (p<0.001), total back pain score (p<0.001), nocturnal pain score (p<0.001), fatigue (p<0.01), and morning stiffness (p<0.001). Pain, fatigue, and morning stiffness were significantly correlated (p<0.001) with baseline values of patient-reported health-related quality of life (HRQOL), and physical function, and with improvements in these values at Week 12 by regression analysis. Treatment effects occurred rapidly (within 2 weeks) and were maintained through 24 weeks of treatment.
Follow-up	24 weeks
Conclusions	Adalimumab significantly improved symptoms of pain, fatigue, and stiffness in patients with AS. Improved symptoms were associated with improved physical function and HRQOL.

Rigby et al., 2011	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=748) ≈ Female, %: Rituximab 1,000 mg MTX group: 84.8, Rituximab 500 mg MTX group: 81.5, Placebo group: 77.1 ≈ Age 48 years ≈ Disease duration, years: Rituximab 1,000 mg MTX group: 0.92, Rituximab 500 mg MTX group: 0.99, Placebo group: 0.91
Intervention(s)	Rituximab 500 mg or 1,000 mg
Intervention(s) characteristics	Patients with active early RA were randomized to groups receiving placebo, rituximab 500 mg, or rituximab 1,000 mg. Rituximab was given by intravenous infusion on days 1 and 15.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Mean FACIT-F scores (~25) at baseline were lower in all 3 treatment groups compared to the published mean for the US general population 43.6±9.4). Relative to patients treated with placebo plus MTX, patients in both rituximab plus MTX dose groups demonstrated a significantly higher improvement in FACIT-F scores from baseline to 52 weeks ($p<0.0001$ for the rituximab 1,000 mg dose and $p<0.05$ for the rituximab 500mg dose). Improvements from baseline in FACIT-F scores were consistent with the observation from the SF-36 vitality domain. In post hoc analyses, a significantly higher proportion of patients receiving rituximab 1,000 mg plus MTX achieved a MCID (≥4) for the FACIT-F from baseline to week 52 compared to the placebo plus MTX group (75.1% vs 67.6%; $p<0.05$). For one additional patient to achieve an improvement in fatigue greater than or equal to the MCID, the NNT was 19.30 (95% CI=7.51 to -33.76) patients for the rituximab 500mg group and 13.37 (95% CI=6.47 to -196.92) patients for the rituximab 1,000 mg group.
Safety results	Not stated in detail
Main results	At week 52, treatment with rituximab in both dose groups showed significant improvements in the HAQ DI compared to the MTX alone group (-0.905 and -0.916 in the rituximab 500 mg plus MTX and 1,000 mg plus MTX groups, respectively, vs -0.628 in the MTX alone group; $p<0.0001$). Higher proportions of patients achieved MCID in the HAQ DI in the rituximab plus MTX groups compared to MTX alone. Treatment with rituximab plus MTX led to a significant reduction in the SF-36 physical component summary for both rituximab dose groups but did not show statistically significant differences in the SF-36 mental component summary. Compared to the MTX alone group, both doses of rituximab plus MTX were associated with significant reductions in the patient global assessment of disease activity and pain, and a significantly higher improvement in Functional Assessment of Chronic Illness Therapy–Fatigue scores from baseline to 52 weeks.
Follow-up	52 weeks
Conclusions	Rituximab plus MTX was associated with significant improvement in physical function and HRQOL outcomes compared with MTX alone in patients previously untreated with MTX.

Ritchlin et al., 2014	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=312) ≈ Female, %: Ustekinumab 90 mg group: 53.3, Ustekinumab 45 mg group: 53.4, Placebo group: 51 ≈ Age, years: Ustekinumab 90 mg group: 48, Ustekinumab 45 mg group: 49, Placebo group: 48 ≈ Disease duration, years: Ustekinumab 90 mg group: 4.5, Ustekinumab 45 mg group: 5.3, Placebo group: 5.5
Intervention(s)	Ustekinumab 45 mg or 90 mg
Intervention(s) characteristics	Adults with active PsA were randomised (stratified by site, weight (≤100 kg/ >100 kg), methotrexate use) to ustekinumab 45 mg or 90 mg at week 0, week 4, q12 weeks or placebo at week 0, week 4, week 16 and crossover to ustekinumab 45 mg at week 24, week 28 and week 40. At week 16, patients with <5% improvement in tender/swollen joint counts entered blinded early escape (placebo→45 mg, 45 mg→90 mg, 90 mg→90 mg).
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Nearly half of the ustekinumab-treated patients achieved a clinically meaningful improvement from baseline to week 24 in FACIT-Fatigue score compared with approximately one-quarter of placebo-treated patients. Changes FACIT-Fatigue scores from baseline were 3 in combined UST group, 3 in 90 mg UST group, 3 in 45 mg UST group and 0 in placebo group (p<0.01).
Safety results	Among ustekinumab-treated and placebo-treated patients, 61.8% and 54.8% reported AEs, 27.1% and 24.0% had investigator-reported infections, 1.9% and 7.7% discontinued study agent because of an AE, and 0.5% and 4.8% had serious AEs, respectively, through week 16. Serious AE rates in ustekinumab-treated patients receiving and not receiving MTX were 3.4% and 7.1%, respectively. No patients died, and no cases of TB were reported through week 60.
Main results	More ustekinumab-treated (43.8% combined) than placebo-treated (20.2%) patients achieved ACR20 at week 24 (p<0.001). Significant treatment differences were observed for week 24 HAQ-DI improvement (p<0.001), ACR50 (p≤0.05) and PASI75 (p<0.001); all benefits were sustained through week 52. Among patients previously treated with ≥1 TNF inhibitor, sustained ustekinumab efficacy was also observed (week 24 combined vs placebo: ACR20 35.6% vs 14.5%, PASI75 47.1% vs 2.0%, median HAQ-DI change −0.13 vs 0.0; week 52 ustekinumab-treated: ACR20 38.9%, PASI75 43.4%, median HAQ-DI change −0.13). No unexpected adverse events were observed through week 60.
Follow-up	52 weeks
Conclusions	The interleukin-12/23 inhibitor ustekinumab (45/90 mg q12 weeks) yielded significant and sustained improvements in PsA signs/symptoms in a diverse population of patients with active PsA, including anti-TNF-experienced PsA patients.

Russell et al., 2007	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=652) ≈ Female 79.2% ≈ Age 51.5 years ≈ Disease duration 8.6 years According to the American Rheumatism Association
Intervention(s)	Abatacept
Intervention(s) characteristics	Abatacept was given by intravenous infusion in a fixed dose of 10 mg/kg at days 1, 15, 29, and every 28 days thereafter for up to 1 year. All patients received MTX (≥15 mg/ week) for the duration of the study. Before day 169, no adjustments in MTX dose were allowed other than for toxicity.
Control	Placebo
Outcomes of interest (types and measuring instruments)	VAS – Fatigue Fatigue was a secondary outcome
Effectiveness results	Fatigue scores declined (indicating improvement) from baseline significantly more in the abatacept group than in the placebo group by day 29 ($F=8.64$; $p<0.01$; partial $\eta^2=0.008$), which was consistent with the observation from the SF-36 vitality domain.
Safety results	Not stated
Main results	Statistically significant improvements in the abatacept group relative to controls were observed across a range of HRQoL measures, including physical function, fatigue, all eight domains of the SF-36, and the physical and mental component summaries (PCS and MCS). Improvements were seen as early as day 29 for fatigue and for five out of eight SF-36 domains. By day 169, all HRQoL measures were significantly better with abatacept than with placebo. HRQoL gains were associated with greater ACR clinical improvement, and the effects were consistent for patients with different disease duration. A significantly greater percentage of patients treated with abatacept reached normative levels of PCS, MCS, physical functioning, and fatigue compared with patients treated with MTX alone.
Follow-up	12 months
Conclusions	Combined abatacept and MTX treatment produces significant improvements across a wide range of HRQoL domains in patients with RA.

Schiff et al., 2017	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=584) ≈ Female, %: Baricitinib 4 mg + MTX group: 73, Baricitinib 4 mg: 76, Placebo group: 70 ≈ Age, years: Baricitinib 4 mg + MTX group: 48.5, Baricitinib 4 mg: 50.9, Placebo group: 50.5 ≈ Disease duration, years: Baricitinib 4 mg + MTX group: 1.3, Baricitinib 4 mg: 1.9, Placebo group: 1.3
Intervention(s)	Baricitinib 4 mg + MTX group or Baricitinib 4 mg
Intervention(s) characteristics	Patients were randomized 4:3:4 to receive oral MTX monotherapy (administered orally once weekly), baricitinib monotherapy (4 mg once daily (QD)), or the combination of baricitinib (4 mg QD) and MTX (baricitinib + MTX). Methotrexate was initiated at 10 mg/week and, if tolerated, increased to 20 mg/week by week 8. A lower dose of MTX was available for patients in whom a lower dose was clinically indicated or required by national guidelines (initial dose of 7.5 mg and a maximum dose of 12.5 mg). Rescue treatment (baricitinib + MTX) was available, beginning at week 24, for those patients whose tender and swollen joint counts did not improve by ≥20% from baseline.
Control	Placebo (Only MTX)
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	Compared to MTX monotherapy, statistically significant improvements in the FACIT-F for both baricitinib groups were observed as early as the first assessment at week 1 ($p \leq 0.001$ for both baricitinib groups vs MTX). The improvements in the FACIT-F score and reductions in duration of MJS, worst joint pain, and worst tiredness were maintained to week 24 and week 52 in both baricitinib groups. The percentage of patients with improvement in the FACIT-F that exceeded the MCID at week 24 (≥3.56) was 65%, 75%, and 71% for MTX, baricitinib monotherapy, and baricitinib + MTX, respectively, at week 24 ($p \leq 0.05$ for baricitinib monotherapy vs MTX; $p=0.268$ for baricitinib + MTX vs MTX). The percentage of patients with improvement in the FACIT-F that exceeded the MCID (≥3.56) was 54%, 62%, and 62%, respectively at week 52 (neither baricitinib group was statistically significantly different from the MTX group).
Safety results	The rates of serious adverse events (AEs) were similar across treatment groups, while rates of some treatment-emergent AEs, including infections, were increased with baricitinib plus MTX. Three deaths were reported, all occurring in the MTX monotherapy group. Malignancies, including nonmelanoma skin cancer, were reported in 1 patient receiving MTX monotherapy, 1 receiving baricitinib monotherapy, and 4 receiving baricitinib plus MTX.
Main results	Compared to MTX, patients in both baricitinib groups reported greater improvement ($p \leq 0.01$) in HAQ-DI, PtGA, pain, fatigue, worst join pain, SF-36 physical component score, and EQ-5D at weeks 24 and 52. For the SF-36 mental component score, patients in both baricitinib groups reported statistically significant improvements ($p \leq 0.01$) at week 52 compared to MTX-treated patients. Statistically significant improvements ($p \leq 0.05$) were observed with the WPAI-RA for the baricitinib groups vs. MTX at week 24 and for the WPAI-RA daily activity and work productivity measures for baricitinib + MTX at week 52.
Follow-up	24 weeks
Conclusions	In this study, baricitinib alone or in combination with MTX, when used as initial therapy, resulted in significant improvement compared to MTX in the majority of the pre-specified PRO measures.

Seitsalo et al., 2007	
Participants characteristics (number, age, disease criteria, details)	Primary Sjögren's syndrome (SS) patients (n=22) ≈ Female, %: not stated ≈ Age, years: not stated ≈ Disease duration, years: not stated
Intervention(s)	Low-dose doxycycline (LDD)
Intervention(s) characteristics	22 patients were randomly assigned to receive either 20 mg LDD or matching placebo twice a day for 10 weeks. The first medication period was followed by 10-week washout period, after which the patient received either LDD or placebo, depending on the first drug received, followed by the second washout period. Stimulated saliva flow rates and pH were measured before and after one and ten weeks of each medication and after washout periods.
Control	Placebo
Outcomes of interest (types and measuring instruments)	VAS -Fatigue Fatigue was a secondary outcome
Effectiveness results	Remarkably similar distribution of VAS scores of fatigue for LDD and placebo throughout both medication periods were observed, with no apparent changes during either medication or between the medications. With the other symptoms evaluated, similar distribution of scores was observed (data not shown). Comparison of the VAS scores between LDD and placebo after seven weeks of medication demonstrated statistically significantly higher VAS scores for fatigue after LDD medication ($p<0.05$ in both cases).
Safety results	Not stated
Main results	Overall, the effects of medications on subjective symptoms were minor. Wilcoxon test demonstrated increased fatigue with LDD during medication ($p<0.05$). The differences may, however, reflect normal fluctuation of symptoms in SS patients.
Follow-up	10 weeks
Conclusions	LDD may not be useful in reducing the primary SS symptoms.

Sieper et al., 2015	
Participants characteristics (number, age, disease criteria, details)	axSpA patients (n=325) ≈ Female 38.5% ≈ Age 39.6 years ≈ Disease duration 7.7 years (median) According to modified New York criteria
Intervention(s)	Certolizumab pegol (CZP)
Intervention(s) characteristics	Patients were randomized 1:1:1 to placebo or CZP 400 mg at weeks 0, 2, and 4 (loading dose), followed by either CZP 200 mg every 2 weeks or CZP 400 mg every 4 weeks. Patients receiving placebo who did not achieve an Assessment of SpondyloArthritis International Society criteria for 20% improvement (ASAS20) in disease activity response at both weeks 14 and 16 were re-randomized 1:1 at week 16 to either CZP 200 mg every 2 weeks or CZP 400 mg every 4 weeks, following the CZP loading dose.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue – NRS Fatigue was a secondary outcome
Effectiveness results	Treatment with CZP also led to relief in fatigue compared to placebo, from week 1 to week 24.
Safety results	Adverse events were reported in 70.4% vs 62.6%, and serious adverse events in 4.7% vs 4.7% of All CZP vs placebo groups. No deaths or malignancies were reported.
Main results	Patients treated with CZP reported significant improvements from week 1 for nocturnal back pain (placebo 20.6, CZP 200 mg every 2 weeks -1.9, and CZP 400 mg every 4 weeks -1.6; $p<0.001$) and ASQOL (placebo -1.0, CZP 200 mg every 2 weeks -2.3, and CZP 400 mg every 4 weeks -1.9; $p<0.05$) compared with placebo, while significant improvements in total back pain were seen from day 2. Patients treated with both CZP dosing regimens also had significantly greater improvements in fatigue, MOS-SPI, SF-36 PCS, MCS, and domains compared with placebo. Improvements were similar in both AS and non-radiographic axial SpA patients.
Follow-up	24 weeks
Conclusions	Both CZP dosing schedules rapidly improved patient well-being, as measured by PROs, including pain, fatigue, sleep, SF-36, and ASQOL in both AS and nonradiographic axial SpA patients

Smolen et al., 2008	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=622) ≈ Female, %: Tocilizumab 4 mg/kg group: 82, Tocilizumab 4 mg/kg group: 85, Placebo group: 78 ≈ Age, years: Tocilizumab 4 mg/kg group: 51.4, Tocilizumab 4 mg/kg group: 50.8, Placebo group: 50.6 ≈ Disease duration, years: Tocilizumab 4 mg/kg group: 7.4, Tocilizumab 4 mg/kg group: 7.5, Placebo group: 7.8 According to American College of Rheumatology (ACR) criteria
Intervention(s)	Tocilizumab
Intervention(s) characteristics	Patients were randomly assigned to receive placebo, tocilizumab 4 mg/kg, or tocilizumab 8 mg/kg intravenously at baseline and thereafter every 4 weeks for 24 weeks in combination with weekly administration of their stable dose of methotrexate (10–25 mg). Randomisation was done centrally with an interactive voice response system, stratified by site with a randomisation list provided by Roche. To minimise methotrexate-related toxicity, all patients received a stable dose of folic acid (≥5 mg/week).
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	There were greater improvements from baseline in FACIT-Fatigue scores over time with both doses of tocilizumab than with placebo. Difference from placebo group was 3.3 (0.9 to 5.6, p=0.0063) in Tocilizumab 4 mg/kg group, and 4.6 (2.3 to 6.9, p<0.0001) in Tocilizumab 8 mg/kg group.
Safety results	More patients receiving tocilizumab reported at least one adverse event than did those receiving placebo. Adverse events with a cumulative incidence by week 24 of 5% or more. More infections were seen in the tocilizumab groups than in the placebo group; the rate of all infections was 98.7 per 100 patient-years of treatment in the 4 mg/kg group, 101.9 per 100 patient-years in the 8 mg/kg group, and 96.1 per 100 patient-years in the placebo group. Cutaneous adverse events were more frequent during treatment with tocilizumab than with placebo. Such events were characterised as mild, self-limited, and of short duration and included localised rashes and dermatitis with or without pruritus; most occurred only once and did not prevent further treatment. There was no apparent association between the rashes and the few hypersensitivity events recorded.
Main results	The intention-to-treat analysis population consisted of 622 patients: one patient in the 4 mg/kg group did not receive study treatment and was thus excluded. At 24 weeks, ACR20 responses were seen in more patients receiving tocilizumab than in those receiving placebo (120 [59%] patients in the 8 mg/kg group, 102 [48%] in the 4 mg/kg group, 54 [26%] in the placebo group; OR=4.0, 95% CI=2.6 to 6.1, p<0.0001 for 8 mg/kg vs placebo; and 2.6 [1.7 to 3.9], p<0.0001 for 4 mg/kg vs placebo). More people receiving tocilizumab than those receiving placebo had at least one adverse event (143 [69%] in the 8 mg/kg group; 151 [71%] in the 4 mg/kg group; 129 [63%] in the placebo group). The most common serious adverse events were serious infections or infestations, reported by six patients in the 8 mg/kg group, three in the 4 mg/kg group, and two in the placebo group.
Follow-up	24 weeks
Conclusions	Tocilizumab could be an effective therapeutic approach in patients with moderate to severe active rheumatoid arthritis.

Smolen et al., 2009	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=461) ≈ Female, %: Golimumab 100 mg group: 80, Golimumab 50 mg group: 74, Placebo group: 85 ≈ Age, years: Golimumab 100 mg group: 55, Golimumab 50 mg group: 55, Placebo group: 54 ≈ Disease duration, years: Golimumab 100 mg group: 8.7, Golimumab 50 mg group: 9.6, Placebo group: 9.8 According to American College of Rheumatology (ACR) criteria
Intervention(s)	Golimumab
Intervention(s) characteristics	Patients were randomly assigned in a 1:1:1 ratio to receive subcutaneous injections of placebo, 50 mg golimumab, or 100 mg golimumab every 4 weeks. Golimumab and placebo were supplied in identical single-use vials. Every patient received a 0.5 mL and a 1 mL injection every 4 weeks. Patients in the 50 mg group received golimumab in the 0.5 mL syringe and placebo in the 1 mL syringe, whereas those in the 100 mg group received golimumab in the 1 mL syringe and placebo in the 0.5 mL syringe. Patients in the placebo group received placebo in both syringes. At week 16, patients in the placebo and 50 mg groups who had less than 20% improvement from baseline in both tender and swollen joint counts entered a double-blinded rescue therapy phase to receive 50 mg or 100 mg golimumab, respectively. Patients in the 100 mg group who met the criteria for rescue therapy continued to receive the same dose. Change of treatment to rescue therapy was not possible at any other time point.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a <u>secondary outcome</u>
Effectiveness results	Treatment with golimumab significantly improved fatigue compared with placebo. Improvement of FACIT-F scores from baseline at weeks 14 and 24 was significantly higher for patients on golimumab than on placebo.
Safety results	Unexpected adverse events or increased frequency of specific adverse events did not occur.
Main results	Patients had discontinued previous TNFα inhibitors because of lack of effectiveness (269 [58%] patients) or reasons unrelated to effectiveness (246 [53%] patients), such as intolerance and accessibility issues. Patients had active disease, which was indicated by a median of 14.0 (IQR=9.0 to 22.0) swollen and 26.0 (16.0 to 41.0) tender joints for the whole group. 28 (18%) patients on placebo, 54 (35%) patients on 50 mg golimumab (OR=2.5, 95% CI=1.5 to 4.2, p=0.0006), and 58 (38%) patients on 100 mg golimumab (2.8 [1.6 to 4.7], p=0.0001) achieved ACR20 at week 14. Two patients were never treated, and 57 patients did not complete the study because of adverse events, unsatisfactory treatment effect, loss to follow-up, death, or other reasons. 155 patients on placebo, 153 on 50 mg golimumab, and 153 on 100 mg golimumab were assessed for drug efficacy. For weeks 1-16, serious adverse events were recorded in 11 (7%) patients on placebo, 8 (5%) on 50 mg golimumab, and 4 (3%) on 100 mg golimumab. For weeks 1-24, after some patients were given rescue therapy, serious adverse events were recorded in 15 (10%) patients on placebo, 14 (5%) on 50 mg golimumab, and 8 (4%) on 100 mg golimumab.
Follow-up	24 weeks
Conclusions	Golimumab reduced the signs and symptoms of rheumatoid arthritis in patients with active disease who had previously received one or more TNFα inhibitors.

Smolen et al., 2017	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=527) ≈ Female, %: Baricitinib 4 mg group: 84, Baricitinib 2 mg group: 79, Placebo group: 82 ≈ Age, years: Baricitinib 4 mg group: 56, Baricitinib 2 mg group: 55, Placebo group: 56 ≈ Disease duration, years: Baricitinib 4 mg group: 12, Baricitinib 2 mg group: 12, Placebo group: 13
Intervention(s)	Baricitinib
Intervention(s) characteristics	Patients were randomly assigned (1:1:1) to receive once-daily placebo or baricitinib 2 or 4 mg in addition to the therapies they were already receiving at enrolment. Patients whose tender and swollen joint counts at baseline were reduced by <20% at both week 14 and week 16 received rescue treatment, baricitinib 4 mg daily
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	Treatment with baricitinib 2 and 4 mg was associated with significant improvements in the FACIT-F at week 4 compared with placebo, the first assessment of this measure. Improvements in the FACIT-F score were sustained to week 12 and week 24. For the FACIT-F, there were more patients in the baricitinib-treated groups who met or exceeded the MCID at week 12 (p=0.004 for baricitinib 2 mg vs placebo and p=0.007 for baricitinib 4 mg vs placebo) as well as at week 24 (p=0.015 for baricitinib 2 mg vs placebo and p=0.005 for baricitinib 4 mg vs placebo).
Safety results	Not stated
Main results	527 patients were randomised (placebo, 176; baricitinib 2 mg, 174; baricitinib 4 mg, 177). Both baricitinib-treated groups showed statistically significant improvements vs placebo in most PROs. Improvements were generally more rapid and of greater magnitude for patients receiving baricitinib 4 mg than 2 mg and were maintained to week 24. At week 24, more baricitinib-treated patients vs placebo-treated patients reported normal physical functioning (HAQ-DI <0.5; p≤0.001), reductions in fatigue (FACIT-F ≥3.56; p≤0.05), improvements in PtGA (p≤0.001) and pain (p≤0.001) and reductions in duration of MJS (p<0.01).
Follow-up	24 weeks
Conclusions	Baricitinib improved most PROs through 24 weeks compared with placebo in this study of treatment-refractory patients with previously inadequate responses to bDMARDs, including at least one TNFi. PRO results aligned with clinical efficacy data for baricitinib.

Stohl et al., 2017	
Participants characteristics (number, age, disease criteria, details)	SLE patients (n=836) ≈ Female, %: Belimumab group: 93.7, Placebo group: 95.7 ≈ Age, years: Belimumab group: 38.1, Placebo group: 39.6 ≈ Disease duration, years (median): Belimumab group: 4.3, Placebo group: 4.6 According to the American College of Rheumatology criteria
Intervention(s)	Belimumab
Intervention(s) characteristics	Patients were randomized 2:1 to receive weekly doses of belimumab 200 mg or placebo administered SC with a prefilled syringe in addition to stable doses of standard SLE therapy. No loading dose was used. Randomization was stratified by a screening SELENA–SLEDAI score (≤9 vs ≥10), complement level (those with vs those without low C3 and/or C4), and race (black vs non-black). Patients must have received a stable SLE medication regimen for at least 30 days prior to enrolment.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Scores on the FACIT-F scale improved over time in both treatment groups. The mean change from baseline was significantly greater in the belimumab group as compared with the placebo group at weeks 8, 36, and 52 (adjusted mean change at week 52 was 4.4 vs 2.7; p=0.0130) but not at weeks 4, 12, and 24. The percentage of patients with an improvement in the FACIT-F score of ≥4 also generally increased over time. At week 52, more patients who received belimumab had an improvement of ≥4 compared with placebo (44.4% vs 36.1%; OR=1.42; 95% CI=1.05 to 1.94; p=0.0245).
Safety results	Overall, 449 patients in the belimumab group (80.8%) and 236 patients in the placebo group (84.3%) experienced at least 1 AE. The most common types were infections and infestations. SAEs were reported for 10.8% and 15.7% of patients, respectively. The most common types were infections and infestations, renal and urinary disorders, and nervous system disorders. Treatment-related AEs were reported for 31.1% of the belimumab group and 26.1% of the placebo group. Local injection site reactions occurred in 34 patients in the belimumab group (6.1%) and 7 patients in the placebo group (2.5%). All were mild or moderate in severity, and no serious or severe injection site reactions were reported.
Main results	A total of 159 patients withdrew before the end of the study. At entry, mean SELENA–SLEDAI scores were 10.5 in the belimumab group and 10.3 in the placebo group. More patients who received belimumab were SRI4 responders than those who received placebo (61.4% vs 48.4%; OR=1.68; 95% CI=1.25 to 2.25; p=0.0006). In the belimumab group, both time to and risk of severe flare were improved (median 171.0 days vs 118.0 days; hazard ratio 0.51; 95% CI=0.35 to 0.74; p=0.0004), and more patients were able to reduce their corticosteroid dosage by ≥25% (to ≤7.5 mg/day) during weeks 40–52 (18.2% vs 11.9%; OR=1.65; 95% CI=0.95 to 2.84; p=0.0732), compared with placebo. AE incidence was comparable between treatment groups; serious AEs were reported by 10.8% of patients taking belimumab and 15.7% of those taking placebo. A worsening of IgG hypoglobulinemia by ≥2 grades occurred in 0.9% of patients taking belimumab and 1.4% of those taking placebo.
Follow-up	52 weeks
Conclusions	In patients with moderate-to-severe SLE, weekly SC doses of belimumab 200 mg plus standard SLE therapy significantly improved their SRI4 response, decreased severe disease flares as compared with placebo, and had a safety profile similar to placebo plus standard SLE therapy.

Strand et al., 2009	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=982) ≈ Female 82% ≈ Age 52 years ≈ Disease duration 6.2 years According to the American College of Rheumatology 1987 RA criteria
Intervention(s)	Certolizumab pegol (CZP)
Intervention(s) characteristics	Patients with active RA were randomized 2:2:1 to subcutaneous CZP (400 mg at weeks 0, 2 and 4; followed by CZP 200 mg or 400 mg) plus methotrexate (MTX) every other week, or placebo (PBO) plus MTX.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue Assessment Scale (FAS) Fatigue was a secondary outcome
Effectiveness results	Statistically significant and clinically meaningful reductions in fatigue were reported by more patients treated with CZP plus MTX than PBO plus MTX throughout the study ($p<0.001$). At week 1, mean changes from baseline in FAS were -1.3 and -1.2 for CZP 200 mg and 400 mg plus MTX, respectively, compared with -0.5 for the PBO plus MTX group ($p<0.001$), and by the end of the study (week 52), mean changes from baseline were -2.6, -2.5 and -0.8, respectively ($p<0.001$). Statistically more CZP plus MTX patients also reported reductions in fatigue equal to or greater than the MCID compared with PBO plus MTX ($p<0.001$). At week 52, 48.9% and 48.6% of CZP 200 mg and 400 mg treated patients reported fatigue reductions equal to or greater than the MCID compared with only 12.6% of PBO treated patients ($p<0.001$).
Safety results	Not stated
Main results	Patients treated with CZP plus MTX reported significant ($p<0.001$), clinically meaningful improvements in HRQoL at the first assessment (week 12); reductions in fatigue, disease activity and pain and improvements in physical function were reported at week 1. In particular, CZP-treated patients reported improvements in mental health. Mean changes from baseline in the SF-36 Mental Component Summary (MCS) at week 52 for CZP 200 mg and 400 mg plus MTX, and PBO plus MTX were 6.4, 6.4 and 2.1, respectively ($p<0.001$). In addition, mental health and vitality scores in CZP-treated patients approached age- and gender-adjusted US population norms. Improvements in all PROs were sustained. Similar benefits were reported with both CZP doses. Changes in SF-36 MCS scores had the lowest correlation with disease activity scores (DAS28) and American College of Rheumatology 20% improvement (ACR20) response rates, while improvements in pain showed the highest correlation.
Follow-up	52 weeks
Conclusions	Treatment with CZP plus MTX resulted in rapid and sustained improvements in all PROs, indicating that the benefits of CZP extend beyond clinical efficacy endpoints into areas that are more relevant and meaningful for patients daily.

Strand et al., 2011	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=619) ≈ Female 82% ≈ Age 52 years ≈ Disease duration 6.2 years According to the American College of Rheumatology 1987 RA criteria
Intervention(s)	Certolizumab pegol (CZP)
Intervention(s) characteristics	Patients were randomised to receive CZP (400 mg at weeks 0, 2 and 4 followed by CZP 200 mg or 400 mg) plus MTX every 2 weeks, or placebo plus MTX for 24 weeks.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue Assessment Scale (FAS) Fatigue was a secondary outcome
Effectiveness results	CZP treatment was associated with reductions in fatigue as early as week 1, which were statistically significant and clinically meaningful (≥MCID) compared with placebo. Reductions in fatigue were maintained until the end of study at week 24 ($p<0.001$). At week 24, significantly more patients in the CZP plus MTX groups reported improvements ≥MCID in fatigue.
Safety results	Not stated
Main results	CZP 200 and 400 mg plus MTX were associated with rapid, clinically meaningful improvements in all PROs. The NNT for subjects to report changes ≥MCID in up to five PROs was two to three, and five for all six PROs (pain, PtGA, physical function, fatigue and short-form 36-item Physical and Mental Component Summary Scores). More patients with improvements ≥MCID in pain at week 6 than those at week 12 had lower disease activity at week 24. Week 12 pain responders had better clinical outcomes at week 24 than non-responders.
Follow-up	24 weeks
Conclusions	The data demonstrate that CZP provides broad relief from the burden of RA.

Strand et al., 2012a	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=489) ≈ Female, %: Tocilizumab 8 mg/kg group: 84, Tocilizumab 4 mg/kg group: 81, Placebo group: 79 ≈ Age, years: Tocilizumab 8 mg/kg group: 53.9, Tocilizumab 4 mg/kg group: 50.9, Placebo group: 53.4 ≈ Disease duration, years: Tocilizumab 8 mg/kg group: 12.6, Tocilizumab 4 mg/kg group: 11, Placebo group: 11.4
Intervention(s)	Tocilizumab
Intervention(s) characteristics	Patients were randomly assigned to receive 4 or 8 mg/kg tocilizumab or placebo (control) i.v. once every 4 weeks and stable doses (1025 mg) of weekly MTX for 24 weeks. Patients without 520% improvement in tender joint count and swollen joint count at week 16 were eligible to receive rescue treatment
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	Mean improvements from baseline to week 24 in FACIT-F scores were 6.66 (>1.5x MCID) with 4 mg/kg and 8.83 (>2x MCID) with 8 mg/kg compared with 4.22 with control (p=0.015 for 8 mg/kg vs controls). Differences between the treatment and control groups were evident starting at 4 weeks.
Safety results	The most common adverse events with higher incidence in tocilizumab groups were infections, gastrointestinal symptoms, rash, and headache. The incidence of serious adverse events was higher in controls (11.3%) than in the 8 mg/kg (6.3%) and 4 mg/kg (7.4%) groups.
Main results	At week 24, 8 mg/kg resulted in significantly greater improvements vs placebo in pain, global assessment of disease activity (p=0.001), Health Assessment Questionnaire-Disability Index (HAQ-DI; p<0.0001), Functional Assessment of Chronic Illness Therapy-Fatigue (p=0.02) and Medical Outcomes Survey Short Form 36 (SF-36 v2) Physical Component Summary (PCS; p=0.0003) scores, all greater than MCID; 4 mg/kg resulted in greater improvements in pain (p=0.01), HAQ-DI (p=0.0030) and SF-36 PCS (p=0.002) scores. Tocilizumab-associated improvements were evident as early as week 2. At week 24, more tocilizumab-treated than control patients reported improvements greater than or equal to MCID in SF-36 domain scores and related PROs (50.9 to 84.9% vs 35.0 to 51.7%) and achieved ACR50 responses and/or Disease Activity Score 28 (DAS28) remission with PRO improvements greater than or equal to MCID (36.2 to 51.2% vs 10 to 20.7% and 10.7 to 37.5% vs 0.0 to 3.4%, respectively).
Follow-up	24 weeks
Conclusions	Tocilizumab treatment in patients with inadequate responses to TNF is resulted in rapid and sustained improvements in multiple PROs that were statistically significant and clinically meaningful, consistent with previous efficacy reports.

Strand et al., 2012b	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=799) ≈ Female, %: Adalimumab plus MTX group: 72, MTX monotherapy group: 73.9, Adalimumab monotherapy group: 77.4 ≈ Age, years: Adalimumab plus MTX group: 51.9, MTX monotherapy group: 52, Adalimumab monotherapy group: 52.1 ≈ Disease duration 9 months
Intervention(s)	Adalimumab plus methotrexate (MTX)
Intervention(s) characteristics	MTX-naive patients ≥ 18 years of age with active RA (≥ 8 swollen joints, ≥ 10 tender joints, and an erythrocyte sedimentation rate ≥ 28 mm/h or C-reactive protein concentration ≥ 1.5 mg/dl, in addition to rheumatoid factor positivity or ≥ 1 joint erosion) and disease duration < 3 years were randomized to receive adalimumab 40 mg subcutaneously every other week plus weekly oral MTX, adalimumab monotherapy, or MTX monotherapy.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	**Adalimumab combination therapy vs MTX monotherapy:** Treatment with adalimumab plus MTX was associated with significant main treatment effects for SF-6D (p=0.02), FACIT-F (p<0.0001), and HUI-3 (p=0.0034) scores and treatment-by-week interactions for SF-6D (p<0.0001) and FACIT-F (p=0.001) scores. **Adalimumab monotherapy vs MTX monotherapy:** No significant differences between the monotherapy groups were observed on the FACIT-F
Safety results	The adverse event profiles were comparable in all 3 groups.
Main results	Of 799 patients enrolled, 268 received adalimumab plus MTX, 257 received MTX monotherapy, and 274 received adalimumab monotherapy. Patients treated with adalimumab plus MTX demonstrated significant baseline to Week 104 improvements in HAQ-DI (p<0.0001), SF-36 Physical Component Summary (p<0.0001), 4 SF-36 domains [physical function (p<0.0001), bodily pain (p<0.0001), vitality (p=0.0139), role limitations-physical (p=0.0005)], SF-6D (p=0.0152), VAS-PtGA (p<0.0001), VAS-pain (p<0.0001), FACIT-F (p<0.0001), and HUI-3 (p=0.0034) scores vs patients treated with MTX monotherapy. Both SF-6D and HUI-3 were found to be sensitive preference-based measures for assessing the effects of treatment on multidimensional function. No clinically meaningful differences between adalimumab and MTX monotherapy groups were observed for most measures. For each measure, there was significant association between HRQOL improvement and ACR clinical response.
Follow-up	2 years
Conclusions	Adalimumab plus MTX significantly improved physical functioning and HRQOL in patients with early RA over 2 years of treatment.

Strand et al., 2014	
Participants characteristics (number, age, disease criteria, details)	SLE patients: BLISS-52 (N=865), BLISS-76 (N=819) ≈ Female, %: BLISS-52: 94.9, BLISS-76: 93.3 ≈ Age, years: BLISS-52: 35.5, BLISS-76: 40.2 ≈ Disease duration, years: BLISS-52: 5.3, BLISS-76: 7.5
Intervention(s)	Belimumab
Intervention(s) characteristics	In addition to standard therapy, patients were randomly assigned to receive placebo, or belimumab 1 or 10 mg/kg. These studies were designed to compare belimumab with placebo, as all patients were receiving active therapy prior to enrolment and during the trials. Treatments were administered intravenously on days 0, 14 and 28, and every 28 days thereafter through week 48 in BLISS-52 and week 72 in BLISS-76.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Although FACIT-Fatigue scores were not significantly different across treatment groups at the week-24 prespecified secondary endpoint, scores from baseline to week 52 improved significantly ($p<0.05$) with belimumab 1 and 10 mg/kg vs placebo in BLISS-52, and with 1 mg/kg at weeks 52 and 76 secondary endpoints in BLISS-76. While differences observed between belimumab 10 mg/kg and placebo were not statistically and at week 52 with both 1 mg/kg (9.78±0.80; $p<0.001$) and 10 mg/kg (9.40±0.87; $p<0.01$). The coefficient of correlation between FACIT-Fatigue and the SF-36 vitality domain was 0.6998 at week 52.
Safety results	Not stated
Main results	Baseline SF-36 scores were 1.5 SDs below age-/sex-matched US norms with similar improvement at week 24 across treatment groups. Mean changes from baseline in PCS scores were significantly ($p<0.05$) greater with belimumab 1 mg/kg (4.20) and 10 mg/kg (4.18) vs placebo (2.96) in BLISS-52, week 52. In BLISS-76, significantly ($p<0.05$) greater improvements were seen with belimumab 1 mg/kg in PCS (belimumab 1 mg/kg=4.37, 10 mg/kg=3.41 vs placebo=2.85) and Mental Component Summary (MCS) scores (belimumab 1 mg/kg=3.14, 10 mg/kg=2.70 vs placebo=1.40) at week 52, and in MCS score at week 76 (belimumab 1 mg/kg=3.05, 10 mg/kg=2.28 vs placebo=1.36). In pooled analysis, significantly greater improvements in PCS, SF-36 vitality domain, and FACIT-Fatigue scores at week 52 were evident with both belimumab doses.
Follow-up	76 weeks
Conclusions	The clinically meaningful improvements in HRQOL in autoantibody-positive patients with active SLE treated with belimumab and standard therapy are consistent with the reductions in disease activity observed in these trials.

Strand et al., 2015	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=399) ≈ Female 84% ≈ Age 54.4–55.4 years ≈ Disease duration 11.3–13.0 years
Intervention(s)	Tofacitinib
Intervention(s) characteristics	Patients were randomized 2:2:1:1 to receive tofacitinib 5 mg or 10 mg BID, placebo advanced to tofacitinib 5 mg BID, or placebo advanced to tofacitinib 10 mg BID. All patients receiving placebo were blindly advanced to tofacitinib at month 3.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Significant improvements vs placebo in FACIT-F was observed at month 3 with tofacitinib 5 mg and 10 mg BID. Improvements from baseline in FACIT-F, which was measured at month 3 and month 6, remained significant (vs placebo) at month 6. At month 3, LS mean changes from baseline exceeded minimal clinically important differences (MCID) in FACIT-F (≥4 points) for both tofacitinib doses. The proportion of patients reporting improvements ≥MCID was also significantly higher for FACIT-F in the tofacitinib 5 mg treatment group vs placebo.
Safety results	Safety was consistent with phase 2 and 3 studies. The most common adverse events in months 0–3 were diarrhoea (13 of 267; 4.9%), nasopharyngitis (11 of 267; 4.1%), headache (11 of 267; 4.1%), and urinary tract infection (eight of 267; 3.0%) across tofacitinib groups, and nausea (nine of 132; 6.8%) in the placebo group.
Main results	Patients received tofacitinib 5 mg (n=133) or 10 mg (n=134), or placebo advanced to tofacitinib 5 mg (n=66) or 10 mg (n=66). HAQ-DI, PtGA ($p<0.0001$), and SF-36 physical and mental component ($P<0.05$) scores were improved for both tofacitinib doses vs placebo. Furthermore, improvements ≥minimum clinically important difference were more frequently reported by tofacitinib-treated patients vs placebo: PtGA ($p<0.05$), pain ($p<0.0001$), HAQ-DI ($p<0.05$), SF-36 physical and mental component scores ($p<0.05$), and FACIT-F ($p<0.001$ for 5 mg BID). No statistical differences were observed in the MOS Sleep Scale.
Follow-up	6 months
Conclusions	Tofacitinib treatment resulted in significant, clinically meaningful improvements in multiple PROs vs placebo over 3 months' treatment in patients with active RA and previous inadequate response to TNFi.

Strand et al., 2016a	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=792) ≈ Female 77.4–83.8% ≈ Age ranged 51.9– 52.7 years ≈ Disease duration 8.1–9.9 years
Intervention(s)	Tofacitinib
Intervention(s) characteristics	Patients (n= 795) with active RA and previous inadequate response to therapy with ≥ 1 conventional or biologic DMARD were randomized 4:4:1:1 to tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, placebo advanced to 5 mg BID, or placebo to 10 mg BID, in combination with stable background DMARD therapy.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Patients receiving both doses of tofacitinib reported significantly greater improvements ($p<0.0001$) from baseline in FACIT-F at month 3 vs placebo. Improvement in fatigue was sustained to month 12.
Safety results	Not stated
Main results	At month 3, statistically significant improvements from baseline vs placebo were reported in PtGA, Pain, HAQ DI, all 8 SF-36 domains, FACIT-F, and MOS Sleep with tofacitinib 10 mg BID, and in PtGA, Pain, HAQ DI, 7 SF-36 domains, FACIT-F, and MOS Sleep with tofacitinib 5 mg BID. Improvements were sustained to month 12. Significantly more tofacitinib-treated patients reported improvements of greater than or equal to the minimum clinically important differences at month 3 vs placebo in all PROs, except the SF-36 role-emotional domain (significant for tofacitinib 10 mg BID).
Follow-up	12 months
Conclusions	Patients with active RA treated with tofacitinib combined with background conventional DMARD therapy reported sustained, significant, and clinically meaningful improvements in PROs vs placebo.

Strand et al., 2016b	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=717) ≈ Female 75.0-85.3% ≈ Age ranged 51.9– 55.5 years ≈ Disease duration 6.9–9.0 years According to ACR 1987 Revised Criteria
Intervention(s)	Tofacitinib or adalimumab
Intervention(s) characteristics	Patients were randomized to receive oral tofacitinib 5 or 10mg BID, adalimumab 40mg subcutaneous injection self-administered once every 2 weeks, or placebo (advanced to either tofacitinib 5 or 10 mg BID). All patients had received 7.525 mg of MTX weekly with sufficient residual disease activity to meet entry criteria.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	LSM changes from baseline at month 3 in FACIT-F were statistically significant vs placebo with tofacitinib 5 and 10 mg BID; LSM changes in FACIT-F were significant vs placebo with adalimumab. Improvement in fatigue was maintained through month 12. Fluctuations observed in the placebo to 5 mg BID and placebo to 10 mg BID groups between months 13 and months 36 reflected improvement and stabilization post-month 6, when all patients received active treatment. More patients receiving tofacitinib 5 mg BID (55.98%; $p<0.001$ vs placebo), 10 mg BID (59.56%; $p<0.0001$ vs placebo) or adalimumab (53.19%; $p<0.05$ vs placebo) reported improvements ≥MCID by FACIT-F; NNTs were 4.9, 4.1 and 5.6, respectively.
Safety results	Not stated
Main results	At month 3, tofacitinib 10 mg BID treatment resulted in significant changes from baseline vs placebo across all PROs, sustained to month 12, with the highest number of patients reporting improvements 5minimum clinically important differences vs placebo ($p<0.05$). Changes from baseline at month 3 with tofacitinib 5 mg BID and adalimumab were similar and statistically significant vs placebo across most PROs, excluding SF-36 Mental Component Score and Social Functioning, Role Emotional, and Mental Health domains, with significantly more patients reporting improvements 5minimum clinically important differences. Numbers Needed to Treat were lowest for tofacitinib 10 mg BID and similar between tofacitinib 5 mg BID and adalimumab.
Follow-up	12 months
Conclusions	Patients with moderate to severe RA and inadequate responses to MTX reported improvements across a broad range of PROs with tofacitinib 5 and 10 mg BID and adalimumab that were significantly superior to placebo.

Strand et al., 2016c	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=1197) ≈ Female 79.8-84.5% ≈ Age ranged 50.1– 50.9 years ≈ Disease duration 8.6–9.5 years According to ACR 1987 Revised Criteria
Intervention(s)	Sarilumab
Intervention(s) characteristics	Sarilumab is a human monoclonal antibody directed against the alpha subunit of the interleukin-6 receptor complex. Patients were randomized to receive placebo, sarilumab 150 or 200 mg subcutaneously + MTX every 2 weeks for 52 weeks; after 16 weeks, patients without ≥20 % improvement from baseline in swollen or tender joint counts on two consecutive assessments were offered open-label treatment
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	The FACIT-F demonstrated improvement at week 24 with sarilumab 150 mg and 200 mg that was significantly greater than placebo and was maintained through week 52 ($p<0.0001$ for both doses at both time points). Improvements in FACIT-F scores were evident by 2 weeks after the start of treatment.
Safety results	Not stated
Main results	Both doses of sarilumab + MTX vs placebo + MTX resulted in improvement from baseline by week 24 in PtGA, pain, HAQ-DI, SF-36 and FACIT-F scores ($p<0.0001$) that was clinically meaningful and persisted until week 52. In post hoc analyses, the percentages of patients with improvement equal to or greater than the MCID across all PROs were greater with sarilumab than placebo ($p<0.05$), with differences ranging from 11.6 to 26.2%, as were those reporting equal to or greater than normative scores.
Follow-up	52 weeks
Conclusions	Patients with MTX-IR RA, sarilumab + MTX resulted in sustained improvement in PROs that were clinically meaningful, greater than placebo + MTX, and complement the previously reported clinical efficacy and safety of sarilumab.

Strand et al., 2017a	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=546) ≈ Female 81.9% ≈ Age ranged 52.9 years ≈ Disease duration 12.1 years According to ACR/The European League Against Rheumatism (EULAR) 2010 classification criteria
Intervention(s)	Sarilumab
Intervention(s) characteristics	Patients with TNF-IR RA received subcutaneous placebo or sarilumab 150 or 200 mg q2w + csDMARDs for 24 weeks. At week 12 and onwards, patients with <20% improvement from baseline in swollen or tender joint counts for at least two consecutive assessments separated by ≥4 weeks were offered rescue with open-label sarilumab 200 mg q2w
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Greater improvements reported with both sarilumab doses vs placebo at week 12 in FACIT-F ($p<0.05$) were maintained at week 24. Improvements in FACIT-F scores were reported at 2 weeks after start of treatment.
Safety results	Serious infections occurred in 1.1%, 0.6%, and 1.1% of patients receiving placebo, sarilumab 150 mg, and sarilumab 200 mg, respectively. Laboratory abnormalities included decreased absolute neutrophil count and increased transaminase levels in both sarilumab groups compared with placebo. In this study, reductions in the absolute neutrophil count were not associated with an increased incidence of infections or serious infections.
Main results	Sarilumab + csDMARDs doses resulted in improvements from baseline at week 12 vs placebo + csDMARDs in PtGA, pain, HAQ-DI, SF-36 and FACIT-F that were maintained at week 24. Sarilumab improved morning stiffness and reduced the impact of RA on work, family, social/leisure activities participation (WPS-RA) and on patients' lives (RAID). Percentages of patients reporting improvements ≥MCID and ≥ normative scores were greater with sarilumab than placebo.
Follow-up	24 weeks
Conclusions	In patients with TNF-IR RA, 150 and 200 mg sarilumab + csDMARDs resulted in clinically meaningful patient-reported benefits on pain, fatigue, function, participation, and health status at 12 and 24 weeks that exceeded placebo + csDMARDs and were consistent with the clinical profile previously reported.

Strand et al., 2017b	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=606) ≈ Female, %: Secukinumab 150 mg group: 52.5, Secukinumab 75 mg group: 58.4, Placebo group: 52.5 ≈ Age ranged, years: Secukinumab 150 mg group: 49.6, Secukinumab 75 mg group: 48.8, Placebo group: 48.5 ≈ Disease duration: not stated
Intervention(s)	Secukinumab
Intervention(s) characteristics	Subjects were randomised 1:1:1 to receive intravenous (i.v.) secukinumab 10 mg/kg at weeks 0, 2 and 4 followed by subcutaneous secukinumab 150 or 75 mg every 4 weeks or matching placebo until week 24.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Both doses of secukinumab resulted in improvements from baseline in FACIT-Fatigue scores at week 24 compared with placebo.
Safety results	During the 16-week placebo-controlled period, adverse events were reported in 64.9% of patients receiving 150 mg of secukinumab, in 60.4% of those receiving 75 mg of secukinumab, and in 58.4% of those receiving placebo. Rates of nonfatal serious adverse events and discontinuations were similar across the study groups
Main results	At week 24, subjects receiving secukinumab i.v.→150 mg or i.v.→75 mg reported greater least squares mean changes from baseline than those receiving placebo in patient global assessment of disease activity (−20.6 and −20.0 vs −7.4, respectively), patient assessment of pain (−20.8 and −20.4 vs −6.7), psoriatic arthritis quality of life (−3.5 and −3.2 vs −0.4), Dermatology Life Quality Index (−8.8 and −7.9 vs 0.7); p<0.0001 vs placebo for both secukinumab groups for above PROs and Functional Assessment of Chronic Illness Therapy-Fatigue (6.74 (p<0.05 vs placebo) and 6.03 vs 4.00); all of which well exceeded minimum clinically important differences.
Follow-up	24 weeks
Conclusions	In subjects with PsA, secukinumab treatment resulted in clinically meaningful improvements in global disease activity, pain, generic and disease specific measures of health-related quality of life and fatigue.

Strand et al., 2018a	
Participants characteristics (number, age, disease criteria, details)	RA patients: OPTION study (n=409), BREVACTA study (n=656), SUMMACTA study (n=1095) ≈ Female ranged 78-86% ≈ Age ranged 50.6-52.5 years ≈ Disease duration ranged 7.5-11.1 years
Intervention(s)	Tocilizumab (TCZ)-intravenous or TCZ-subcutaneous
Intervention(s) setting	Placebo
Control	TCZ-intravenous or TCZ-subcutaneous
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a <u>secondary outcome</u>
Effectiveness results	In OPTION, 16%-43% of patients treated with TCZ-intravenous every 4 weeks reported scores ≥ normative values across HAQ-DI, FACIT-Fatigue and SF-36 PCS/MCS and 16%-44% across SF-36 domains at week 16 compared with 5%-19%and 8%-28% of placebo-treated patients, respectively. In BREVACTA, the proportion of patients treated with TCZ-subcutaneous every 2 weeks reporting scores ≥ normative values ranged from 8% to 32% for HAQ-DI, FACIT-Fatigue and SF-36 PCS/MCS and from 12% to 34% across SF-36 domains at week 12 compared with 4%-23%and 8%-25% in placebo, respectively. In SUMMACTA, 14%-39% of patients treated with TCZ-subcutaneous weekly and 15%-40% receiving TCZ-intravenous every 4 weeks reported scores ≥ normative values across HAQ-DI and SF-36 PCS/MCS scores at week 24; 19%-44% of patients treated with TCZ-subcutaneous weekly and 20%-42% of patients treated with TCZ-intravenous every 4 weeks reported scores ≥ normative values across SF-36 domains.
Safety results	Not stated
Main results	In OPTION, more patients who received TCZ-intravenous reported improvements in PROs ≥MCID (50%-82% vs 31%-57%) and scores ≥ normative values (16%-44% vs 5%-28%) at week 16 compared with placebo. Similarly, a greater proportion of patients in BREVACTA who received TCZ-subcutaneous reported improvements ≥ MCID (54%-73% vs 42%-55%) and scores ≥ normative values (8%-34% vs 4%-25%) at week 12 compared with placebo. In SUMMACTA, 61%-84% of patients who received TCZ-subcutaneous and 64%-84% of those who received TCZ-intravenous reported improvements ≥ MCID and 14%-41%and 15%-24%, respectively, scores ≥ normative values at week 24.
Follow-up	24 weeks
Conclusions	TCZ-intravenous or TCZ-subcutaneous with csDMARDs resulted in more patients reporting clinically meaningful improvements and PRO scores ≥ normative values compared with placebo. These improvements were similar with TCZ-intravenous and TCZ-subcutaneous.

Strand et al., 2018b	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=369) ≈ Female 83% ≈ Age ranged 52.2 years ≈ Disease duration: 8.1 years in the sarilumab group and 6.6 years in the adalimumab group
Intervention(s)	Sarilumab
Intervention(s) characteristics	Patients with active RA intolerant of, or inadequate responders to, methotrexate were randomized to sarilumab 200 mg plus placebo every 2 weeks (q2w; n = 184) or adalimumab 40 mg plus placebo q2w (n = 185). Dose escalation to weekly administration of adalimumab or matching placebo was permitted at week 16. PROs assessed at baseline and weeks 12 and 24.
Control	Adalimumab
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	At week 24, LSM changes in FACIT-F were not statistically different (p=0.069). At week 24, the percentages of patients reporting scores greater than or equal to normative values in HAQ-DI, FACIT-F, and SF-36 PCS and MCS and all individual SF-36 domains increased with both sarilumab and adalimumab, with numerically greater increases reported with sarilumab than with adalimumab
Safety results	Incidences of infections (sarilumab: 28.8%; adalimumab: 27.7%) and serious infections (1.1%, both groups) were similar, despite neutropenia differences.
Main results	At week 24, sarilumab treatment resulted in significantly greater least-squares mean (LSM) changes from baseline than adalimumab monotherapy in HAQ-DI ($p<0.005$), PtGA ($p<0.001$), pain VAS ($p<0.001$), and SF-36 Physical Component Summary (PCS) ($p<0.001$). Greater LSM changes were reported for sarilumab than for adalimumab in RAID ($p<0.001$), morning stiffness VAS ($p<0.05$), and WPS-RA ($p<0.005$). Between-group differences in FACIT-F and SF-36 Mental Component Summary (MCS) were not significant. More patients reported improvements greater than or equal to the MCID in HAQ-DI ($p<0.01$), RAID ($p<0.01$), SF-36 PCS ($p<0.005$), and morning stiffness ($p<0.05$), as well as greater than or equal to the normative values in HAQ-DI ($p<0.05$), with sarilumab versus adalimumab.
Follow-up	24 weeks
Conclusions	In parallel with the clinical efficacy profile previously reported, sarilumab monotherapy resulted in greater improvements across multiple PROs than adalimumab monotherapy.

Strand et al., 2019a	
Participants characteristics (number, age, disease criteria, details)	Giant cell arteritis (GCA) patients (n=201) ≈ Female, %: TCZ-QW + Pred-26 group: 78, PBO + Pred-26 group: 76, PBO + Pred-52 group: 72.5 ≈ Age, years: TCZ-QW + Pred-26 group: 69.5, PBO + Pred-26 group: 69.3, PBO + Pred-52 group: 67.8 ≈ Disease duration, days: TCZ-QW + Pred-26 group: 306.8, PBO + Pred-26 group: 364.7, PBO + Pred-52 group: 255.2
Intervention(s)	Exploratory analyses of SF-36 PCS and MCS and domain scores, PtGA and FACIT-Fatigue were performed in patients treated with weekly subcutaneous TCZ 162 mg plus 26-week prednisone taper (TCZ-QW + Pred-26) or placebo plus 26-week or 52-week prednisone tapers (PBO + Pred-26 or PBO + Pred-52). These analyses were performed on responder and non-responder patients, including those who achieved the primary outcome and those who experienced flare and received escape prednisone doses.
Intervention(s) characteristics	Patients were randomly assigned (2:1:1:1) to one of four 52-week regimens: (1) weekly subcutaneous TCZ 162 mg plus a 26-week prednisone taper (TCZ-QW + Pred-26), (2) every-other-week subcutaneous TCZ 162 mg plus a 26-week prednisone taper (TCZ-Q2W + Pred-26), (3) weekly subcutaneous placebo plus a 26-week prednisone taper (PBO + Pred-26) or (4) placebo plus a 52-week prednisone taper (PBO + Pred-52).
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a <u>secondary outcome</u>
Effectiveness results	LSM increases in FACIT-Fatigue scores from baseline to week 52 in the TCZ-QW + Pred-26 group were significantly greater than in both PBO + Pred groups ($p<0.001$) and exceeded the MCID
Safety results	Not stated
Main results	Exploratory analyses of SF-36 PCS and MCS and domain scores, PtGA and FACIT-Fatigue were performed in patients treated with weekly subcutaneous TCZ 162 mg plus 26-week prednisone taper (TCZ-QW + Pred-26) or placebo plus 26-week or 52-week prednisone tapers (PBO + Pred-26 or PBO + Pred-52). These analyses were performed on responder and non-responder patients, including those who achieved the primary outcome and those who experienced flare and received escape prednisone doses.
Follow-up	52 weeks
Conclusions	Patients with GCA receiving TCZ-QW + Pred-26 reported statistically significant and clinically meaningful improvement in SF-36 and FACIT-Fatigue scores compared with those receiving prednisone only. Improvements in the TCZ-QW + Pred-26 group led to recovery of HRQOL to levels at least comparable to those of A/G-matched normative values at week 52 and exceeded normative values in five of eight domains.

Strand et al., 2019b	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=422) ≈ Female 53.3% ≈ Age 47.9 years ≈ Disease duration 6.1 years Fulfilled the ClASsification criteria for Psoriatic ARthritis
Intervention(s)	Tofacitinib 5 mg or 10 mg twice daily or adalimumab 40 mg subcutaneously every 2 weeks
Intervention(s) characteristics	Eligible patients were randomised 2:2:2:1:1 to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg subcutaneous injection once every 2 weeks, placebo advancing to tofacitinib 5 mg twice daily at month 3 or placebo advancing to tofacitinib 10 mg twice daily at month 3. Patients received a stable background dose of a single csDMARD (methotrexate: 83.6%; sulfasalazine: 9.2%; leflunomide: 5.7%; hydroxychloroquine: 0.2%; other: 1.2%) and were followed up to month 12.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Greater improvements from baseline in FACIT-Fatigue Total score were reported at month 1 following tofacitinib 5 mg twice daily vs placebo. At month 3, greater improvements from baseline in FACIT-Fatigue Total score were reported by patients receiving both tofacitinib doses, compared with placebo. Patients receiving adalimumab also reported significant improvements in FACIT-Fatigue at month 3, compared with placebo ($p \leq 0.05$). Improvements in FACIT-Fatigue with all active treatments were generally maintained to month 12. Patients receiving placebo who advanced to tofacitinib 5 mg or 10 mg twice daily at month 3 reported improvements in FACIT-Fatigue post-month3. The percentage of patients reporting improvements ≥MCID in FACIT-Fatigue at month 3 were greater with both tofacitinib doses ($p \leq 0.05$) but not with adalimumab vs placebo; number needed to treat (NNTs) were similar across active treatments.
Safety results	Not stated
Main results	At month 3, PtGA, Pain, PGJS, FACIT-Fatigue, EQ-5D-3L, ASQoL and SF-36v2 Physical Component Summary (PCS), physical functioning (PF), bodily pain (BP) and vitality domain scores exceeded placebo with both tofacitinib doses ($p \leq 0.05$); SF-36v2 social functioning with 5 mg twice daily ($p \leq 0.05$). Percentages reporting improvements ≥MCID in PtGA, Pain, PGJS, FACIT-Fatigue, ASQoL and SF-36v2 PCS, PF, BP and general health scores exceeded placebo with both tofacitinib doses ($p \leq 0.05$) and were similar with adalimumab.
Follow-up	3 months
Conclusions	csDMARD-IR patients with active PsA reported statistically and clinically meaningful improvements in PROs with tofacitinib compared with placebo at Month 3.

Strand et al., 2019c	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=394) ≈ Female 55.3% ≈ Age 50.0 years ≈ Disease duration 9.1-9.6 years Fulfilled the ClASsification criteria for Psoriatic ARthritis (CASPAR)
Intervention(s)	Tofacitinib 5 or 10 mg twice daily
Intervention(s) characteristics	Eligible patients were randomised 2:2:1:1 to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo advanced to tofacitinib 5 mg twice daily or placebo advanced to tofacitinib 10 mg twice daily. Placebo groups advanced in a blinded manner to tofacitinib at month 3. All patients continued treatment with a stable dose of a single csDMARD, the most frequent being methotrexate.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Significant improvements from baseline were reported at month 3 with both doses of tofacitinib compared with placebo in FACIT-Fatigue. Patients reported improved FACIT-Fatigue Total scores compared with placebo in both tofacitinib doses at month 1 (earliest time point), maintained to months 3 (all p≤0.05) and 6. Patients advancing from placebo to tofacitinib 5 or 10 mg twice daily reported similar improvements after month 3. While numerically higher compared with placebo, there was no significant difference between the percentages of patients reporting improvements in FACIT-Fatigue Total score ≥MCID in tofacitinib-treated patients. Patients reporting scores ≥normative values were similar for tofacitinib and placebo. Number needed to treat (NNT) values were lower in patients receiving tofacitinib 5 mg twice daily compared with tofacitinib 10 mg twice daily.
Safety results	Not stated
Main results	At month 3, PtGA, Pain, PGJS, SF-36v2 Physical Component Summary (PCS), physical functioning (PF), bodily pain (BP), vitality and social functioning (SF) domains, FACIT-Fatigue Total score, EQ-5D-3L pain/discomfort, EQ-VAS and ASQoL scores exceeded placebo with both tofacitinib doses (role physical [RP] with 10 mg twice daily only; p≤0.05). Patients reporting improvements ≥MCID (%) in PtGA, PGJS, Pain, ASQoL and SF-36v2 PCS, PF, RP, BP, SF (both tofacitinib doses) exceeded placebo (p≤0.05).
Follow-up	6 months
Conclusions	TNFi-IR patients with PsA receiving tofacitinib reported statistically and clinically meaningful improvements in PROs vs placebo over 3 months, which were maintained to month 6. Despite lower baseline scores, these improvements were similar to the csDMARD-IR TNFi-naive OPAL Broaden trial.

Strand et al., 2019d	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=661) ≈ Female, %: Upadacitinib 30 mg group: 78.5, Upadacitinib 15 mg group: 82.4, Placebo group: 75.1 ≈ Age, years: Upadacitinib 30 mg group: 55.8, Upadacitinib 15 mg group: 55.3, Placebo group: 56.0 ≈ Disease duration, years: Upadacitinib 30 mg group: 7.3, Upadacitinib 15 mg group: 7.3, Placebo group: 7.2
Intervention(s)	Upadacitinib 15 mg and 30 mg
Intervention(s) characteristics	Patients were randomly assigned (2:2:1:1) to receive either upadacitinib 15 mg or 30 mg or placebo daily for 12 weeks while continuing background csDMARD therapy. After the initial 12-week placebo-controlled period, patients taking placebo received 15 mg or 30 mg of upadacitinib daily, according to the prespecified randomisation assignment.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	At week 12, significantly ($p<0.05$) more upadacitinib-treated (15 mg and 30 mg) patients reported improvements ≥ MCID in FACIT-F. Differences between the active and placebo treatment groups were statistically significant ($p<0.05$) in FACIT-F with both upadacitinib doses vs placebo.
Safety results	Not stated
Main results	Compared with placebo, patients receiving upadacitinib reported statistically significant improvements (both doses, $p<0.05$) in PtGA, pain, HAQ-DI, FACIT-F, duration and severity of AM stiffness, SF-36 (PCS and 6/8 domains), and RA-WIS at week 12. Significantly, more upadacitinib-treated patients (both doses, $p<0.05$) reported improvements ≥ MCID in PtGA, pain, HAQ-DI, FACIT-F, AM stiffness, SF-36 (PCS and 4 or 7/8 domains), and RA-WIS and scores ≥ normative values in HAQ-DI, FACIT-F, and SF-36 (PCS and 4 or 5/8 domains). For most PROs, the incremental NNT with upadacitinib to report clinically meaningful improvement from baseline ranged from 4 to 8 patients.
Follow-up	12 weeks
Conclusions	Upadacitinib 15 mg or 30 mg daily for 12 weeks resulted in significant and clinically meaningful improvements in global disease activity, pain, physical function, fatigue, duration, and severity of AM stiffness, HRQOL, and work instability among csDMARD-IR patients with RA.

Strand et al., 2020	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=797) ≈ Female, %: Tofacitinib 5 mg BID group: 83.8, Tofacitinib 10 mg BID group: 86.1, Placebo → tofacitinib 5 mg BID group: 80.2, Placebo → tofacitinib 10 mg BID group: 91.1 ≈ Age, years: Tofacitinib 5 mg BID group: 53.7, Tofacitinib 10 mg BID group: 52.0, Placebo → tofacitinib 5 mg BID group: 53.2, Placebo → tofacitinib 10 mg BID group: 52.1 ≈ Disease duration, years: Tofacitinib 5 mg BID group: 8.9, Tofacitinib 10 mg BID group: 9.0, Placebo → tofacitinib 5 mg BID group: 8.8, Placebo → tofacitinib 10 mg BID group: 9.5
Intervention(s)	Tofacitinib 5 or 10 mg BID
Intervention(s) characteristics	Eligible patients were randomised 4:4:1:1 to receive tofacitinib 5 or 10 mg BID, or placebo advanced to tofacitinib (placebo→tofacitinib) 5 or 10 mg BID. The randomisation schedule for the placebo sequences was pre-specified; at month 3, non-responders (defined as <20% improvement in swollen and tender joint counts) were blindly advanced to tofacitinib; at month 6, all remaining patients were blindly advanced to tofacitinib. All patients must have been receiving MTX continuously for ≥4 months with stable doses for ≥6 weeks and continued stable doses (15–25 mg weekly) throughout the study. Weekly doses <15 mg were allowed only if there was documented intolerance to, or toxicity from higher doses, or where higher doses would violate the local label.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Through month 3, patients receiving tofacitinib 5 and 10 mg BID reported significant LSM changes from baseline vs placebo in FACIT-F (both p<0.0001), which were generally sustained through month 24. Once placebo→tofacitinib patients were advanced, they reported generally similar improvements in FACIT-F scores at month 24 to patients who had received tofacitinib throughout the study. A significantly (p<0.0001) greater proportion of tofacitinib- vs placebo-treated patients reported clinically meaningful improvements (≥MCID; 4-point improvement) in FACIT-F at month 3, maintained at months 12 and 24, and increased in placebo→tofacitinib patients, once receiving tofacitinib. Patients receiving tofacitinib 10 mg BID reported numerically greater LSM changes in FACIT-F, with higher proportions of patients with clinically meaningful improvements ≥MCID than tofacitinib 5 mg BID, and lower NNTs (4.0 vs 4.3). At baseline, the proportion of patients reporting scores ≥-normative FACIT-F values (≥43.5 [≥40.1]) were higher for placebo→tofacitinib 5 mg BID (17.7% [20.3%]) and placebo→tofacitinib 10 mg BID patients (15.8% [23.7%]) compared with patients receiving tofacitinib 5 and 10 mg BID (9.5% [13.7%] and 9.4% [15.3%], respectively). However, at month 3, tofacitinib 5 and 10 mg BID groups demonstrated larger increases in proportions of patients reporting scores ≥ normative values (19.3% [31.2%] and 27.3% [38.7%], respectively) than placebo→tofacitinib 5 and 10 mg BID (9.3% [14.7%] and 18.3% [26.8%]). After month 6, all patients were receiving tofacitinib, and at month 12 the proportion of patients with scores ≥-normative FACIT-F values in the placebo→tofacitinib 5 and 10 mg BID sequences (29.9% [34.3%] and 32.3% [40.3%], respectively) met or exceeded tofacitinib 5 or 10 mg BID patients (21.5% [33.5%] and 25.7% [36.6%]). Similar data were reported at month 24, proportions of patients in placebo→tofacitinib 5 and 10 mg BID sequences were generally higher (33.3% [38.9%] and 42.3% [50.0%], respectively) compared with tofacitinib 5 and 10 mg BID (24.9% [36.8%] and 32.4% [44.0%]).
Safety results	Not stated
Main results	Overall, 539/797 (67.6%) patients completed 24 months' treatment. At month 3, tofacitinib-treated patients reported significant (p<0.05) mean changes from baseline vs placebo across all PROs, and significantly more patients reported improvements ≥ minimum clinically important differences vs placebo. Improvements in PROs with tofacitinib were sustained to month 24. Following advancement to tofacitinib, placebo-treated patients generally reported changes of similar magnitude to tofacitinib-treated patients.
Follow-up	24 months
Conclusions	Patients with RA and MTX-IR receiving tofacitinib 5 or 10 mg BID plus MTX reported significant and clinically meaningful improvements in PROs vs placebo at month 3, which were sustained through 24 months.

Strand et al., 2021a	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=641) ≈ Female, %: Upadacitinib 30 mg QD group: 52.8, Upadacitinib 15 mg QD group: 53.6, Placebo group: 56.6 ≈ Age, years: Upadacitinib 30 mg QD group: 53.0, Upadacitinib 15 mg QD group: 53.0, Placebo group: 54.1 ≈ Disease duration, years: Upadacitinib 30 mg QD group: 9.7, Upadacitinib 15 mg QD group: 9.6, Placebo group: 11.0 According to the Classification Criteria for PsA (CASPAR)
Intervention(s)	Upadacitinib 15 mg or 30 mg
Intervention(s) characteristics	Patients were randomized 2:2:1:1 to receive oral upadacitinib 15 mg QD, upadacitinib 30 mg QD, or placebo switched to either upadacitinib 15 mg once daily (QD) or upadacitinib 30 mg QD at week 24. Treatment in the randomized controlled portion of the trial was 24 weeks, with blinding to 56 weeks and an open-label extension up to 5 years.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Compared with placebo, significant improvements from baseline to weeks 12 and 24 were reported with upadacitinib 15 and 30 mg across all PROs ($p<0.05$), nominal except for week 12 multiplicity-controlled endpoints of FACIT-F. In patients receiving placebo who were switched to upadacitinib 15 or 30 mg at week 24, rapid improvements in FACIT-F were reported with similar responses at week 56 to those originally randomized to upadacitinib. At week 12, the proportion of patients receiving upadacitinib 15 mg and 30 mg reporting scores ≥ normative values were 29% and 35%, respectively, in FACIT-F vs 17% with placebo.
Safety results	Not stated
Main results	At weeks 12 and 24, patients treated with either upadacitinib dose reported statistically and nominally significant improvements from baseline across all PROs vs placebo ($p\leq0.05$), except the WPAI absenteeism domain, which were maintained or further improved to week 56. A significantly greater proportion of patients receiving either upadacitinib dose reported improvements ≥MCID and scores ≥ normative values vs placebo (nominal $p\leq0.01$) in most PROs at weeks 12 and 24, with clinically meaningful improvements continuing to week 56. Improvements C MCID were reported as early as week 2 in PtGA, pain, and HAQ-DI.
Follow-up	56 weeks
Conclusions	Upadacitinib provides rapid, clinically meaningful, and sustained improvements in PROs reported by bDMARD-IR PsA patients.

Strand et al., 2021b	
Participants characteristics (number, age, disease criteria, details)	PsA patients (n=1704) ≈ Female, %: Upadacitinib 30 mg QD group: 55.8, Upadacitinib 15 mg QD group: 55.5, Adalimumab 40 mg EOW: 51.7, Placebo group: 49.9 ≈ Age, years: Upadacitinib 30 mg QD group: 49.9, Upadacitinib 15 mg QD group: 51.6, Adalimumab 40 mg EOW: 51.4, Placebo group: 50.4 ≈ Disease duration, years: Upadacitinib 30 mg QD group: 5.9, Upadacitinib 15 mg QD group: 6.2, Adalimumab 40 mg EOW: 5.9, Placebo group: 6.2 According to the Classification Criteria for PsA (CASPAR)
Intervention(s)	Upadacitinib 15 mg or 30 mg
Intervention(s) characteristics	Patients were randomly assigned in a 1:1:1:1 ratio to upadacitinib 15 mg QD, upadacitinib 30 mg QD, placebo followed by upadacitinib 15 mg QD or 30 mg QD (1:1) at week 24, or adalimumab 40 mg EOW.
Control	Adalimumab or placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	At week 12, significantly (nominal $p<0.05$) more patients receiving both doses of upadacitinib reported scores ≥ normative values in PtGA, HAQ-DI, FACIT-F, EQ-5D-5L, SF-36 PCS, and matched normative values in seven SF-36 domains compared with placebo; scores were maintained or improved to week 24.
Safety results	Not stated
Main results	At weeks 12 and 24, upadacitinib treatment resulted in improvements from baseline vs placebo across all PROs as well as improvements vs adalimumab in HAQ-DI and SF-36 Physical Component Summary score (nominal $p<0.05$). Improvements in PtGA, pain, and HAQ-DI were reported as early as week 2. At week 12, significantly (nominal $p<0.05$) more upadacitinib- vs placebotreated patients reported improvements ≥ MCID across all PROs including seven SF-36 domains. The proportions of upadacitinib-treated patients reporting clinically meaningful improvements at week 12 were similar to or greater than with adalimumab and sustained through week 56. Significantly (nominal $p<0.05$) more upadacitinib-treated (both doses) patients reported scores ≥ normative values at week 12 vs placebo, and scores were generally similar to or greater than adalimumab.
Follow-up	24 weeks
Conclusions	Upadacitinib treatment provides rapid, sustained, and clinically meaningful improvements in PROs in non-bDMARD-IR patients with PsA.

Teitsma et al., 2017	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=317) ≈ Female, %: Tocilizumab plus MTX group: 61, Tocilizumab group: 76, MTX group: 64 ≈ Age, years (median): Tocilizumab plus MTX group: 53, Tocilizumab group: 55, MTX group: 54 ≈ Disease duration, days (median): Tocilizumab plus MTX group: 25, Tocilizumab group: 26, MTX group: 27 According to the 1987/2010 classification criteria
Intervention(s)	Tocilizumab (with or without MTX)
Intervention(s) characteristics	Patients were randomized (1:1:1) to initiate MTX, tocilizumab or tocilizumab plus MTX and treated in a step-up method until the treatment target, sustained remission (defined as DAS28 <2.6 and 44 swollen joints for ≥ 24 weeks), was achieved. Tocilizumab (8 mg/kg) was given intravenously every 4 weeks up to a maximum of 800 mg/dose. MTX (orally) was started at 10 mg/week and increased to 30 mg/week with 5 mg every 4 weeks until remission or maximum tolerable dose was reached, and patients received folic acid 5 mg twice per week to reduce MTX-related toxicity.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	Although patients starting with tocilizumab-based strategies reported greater improvements in fatigue during the 2-year study period compared with the MTX strategy, when performing a linear mixed effect model there were no significant differences over time between tocilizumab (p=0.05) and tocilizumab plus MTX (p=0.16) vs MTX alone. There were however significant differences in favour of tocilizumab at week 12 (tocilizumab vs MTX, p = 0.02) and week 24 (tocilizumab vs MTX, p=0.04; tocilizumab plus MTX vs MTX, p=0.04). Proportions of patients achieving MCID were not significantly different between both tocilizumab arms vs the MTX arm (p≥0.19) during follow-up.
Safety results	Not stated
Main results	During the 2-year study period, significant improvements were found in the tocilizumab strategies in the SF-36 physical component score (tocilizumab, p=0.01; tocilizumab plus MTX, p=0.04) and EQ5D score (tocilizumab plus MTX, p=0.02) when compared with the MTX strategy. No significant differences were noted in other PROs (p≥0.05, except for the domain 'identity' in the Illness Perception Questionnaire; tocilizumab vs MTX, p=0.04). The proportions of patients achieving MCID in SF-36 physical component score were significantly higher at 12 and 52 weeks (p≤0.04) in the tocilizumab arms when compared with the MTX arm. At week 24, the proportion achieving MCID in EQ-5D was significantly higher in the tocilizumab plus MTX arm vs the MTX arm (p=0.04).
Follow-up	2 years
Conclusions	Initiation of treat-to-target tocilizumab therapy resulted in significantly improved PROs, especially within the first 24 weeks, when compared with initiation of MTX therapy. Also on the patients' level, initiating tocilizumab may be considered as a valuable strategy in DMARD-naïve patients with early RA.

Theander et al., 2002	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren's syndrome patients (n=87) ≈ Female 91% ≈ Age 62 years (median) ≈ Disease duration 10 years (median) According to the Copenhagen criteria or the European criteria
Intervention(s)	Gammalinolenic acid (GLA; extracted from Evening Primrose Oil)
Intervention(s) characteristics	Two GLA dosages of either 800 mg or 1600 mg daily given as free fatty acid were compared with a placebo emulsion containing mainly corn oil and no GLA. Both dosages are considered as being high, compared with commercially available GLA preparations containing usually 40mg or 80mg GLA / capsule.
Control	Placebo (corn oil)
Outcomes of interest (types and measuring instruments)	VAS – Fatigue Fatigue was a primary outcome
Effectiveness results	The study could not detect any statistically significant changes in the patients' tiredness as expressed by VAS, either in the placebo or in any of the treatment groups at the 3- or 6-months evaluation, compared to baseline. The time needed for sleep and rest for one day did not change significantly in any of the subgroups during the 6 months of treatment. Neither was there any difference in the response when comparing the effects of the higher and the lower dose of GLA treatment or of GLA and placebo treatment. The response rate was similar in the patients with or without signs of autoimmunity.
Safety results	Only mild gastrointestinal side effects were reported, most often subsiding after some weeks despite continuous medication. 53% of the placebo-treated and 56% of the GLA treated patients experienced some sort of gastrointestinal complaints. Some patients complained about weight gain. There was a tendency towards increased weight, especially in the GLA treated patients, who, however, did not reach statistical significance. No significant changes in any of the laboratory parameters were detected during the study.
Main results	No statistically significant improvement was found in fatigue assessed by Visual Analogue Scale (VAS) or in the time needed for sleeping/resting during a 24-hour period. No differences were found between the treatment and placebo group. The same applies to the secondary endpoints: no differences in VAS for eye and mouth dryness or pain, no significant changes in Schirmer-1-test, van Bijsterveld score, unstimulated whole sialometry (UWS), or use of artificial tears or analgesics. Only mild side effects were observed.
Follow-up	6 months
Conclusions	According to our study results GLA (Evening Primrose oil) treatment for fatigue in primary Sjögren's syndrome is ineffective.

Virkki et al., 2010	
Participants characteristics (number, age, disease criteria, details)	Primary Sjogren's syndrome patients (n=107) ≈ Female, %: not stated ≈ Age, years: not stated ≈ Disease duration, years: not stated
Intervention(s)	Dehydroepiandrosterone (DHEA)
Intervention(s) characteristics	The first treatment period was followed by a washout period of 1 month, after which a crossover was carried out so that those who had received DHEA in the first period received placebo in the second, and vice versa. All the patients (n = 107, 7 men) participated in both the DHEA and placebo periods separated by a washout period. A DHEA dose of 50 mg was selected for use in the present study because it has been used for substitution in Addison's disease and was therefore considered sufficient as a substitution dose.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Multiple Fatigue Inventory (MFI-20), Visual Analog Scale (VAS; scale 0 –100) – Fatigue Fatigue was a primary outcome
Effectiveness results	All MFI-20 subscales, as well as the fatigue VAS, improved from baseline levels because of treatment with DHEA and placebo ($p<0.001$). However, relatively few patients reached near-normal general fatigue scores (MFI-20 score 10), 8 patients during the DHEA period and 9 patients during the placebo period, but only one patient scored 10 after both periods. The differences in treatment effect of DHEA and placebo were not significant. Compared with baseline, fatigue scores were also lower after the washout period than at baseline ($p<0.001$). The proportions of those who responded with at least 20% improvement in fatigue were similar for patients receiving DHEA and placebo, ranging from 27% to 39% depending on the subscale used for measurement. Baseline DHEAS levels were similar in the 20% responders and non-responders to DHEA supplementation. Correspondingly, the baseline serum DHEAS levels did not correlate significantly with the changes in fatigue scores following DHEA supplementation. Women in the younger age group (31-50 years, n=27) tended to respond slightly better to both DHEA and placebo than women in the older age group (51-80 years, n=72). However, the differences between DHEA and placebo were not significant.
Safety results	Six patients had adverse events while receiving placebo and 16 patients had adverse events while receiving DHEA. All adverse events were mild or moderate in severity, except for a case of pneumonia and pneumococcal sepsis occurring during placebo not related to the study medication.
Main results	In an intent-to-treat analysis, a 50-mg DHEA substitution dose and placebo similarly improved fatigue. All the MFI-20 subscales and the fatigue VAS improved from the baseline levels because of treatment ($p<0.001$), but with negligible differences between these 2 treatments. The mean between-treatment difference was -0.1 for general fatigue (the primary outcome measure), 0.0 for physical fatigue, 0.0 for mental fatigue, 0.0 for reduced motivation, 0.3 for reduced activity, and 2.2 for the fatigue VAS. None of these differences was statistically significant.
Follow-up	9 months
Conclusions	Substitution treatment with 50 mg of DHEA in DHEA-deficient and severely tired primary SS patients does not help against fatigue better than placebo. This may relate to the prohormone nature of DHEA and its recently described defective intracrine tissue-specific conversion to active sex steroids in SS.

Wanders et al., 2004	
Participants characteristics (number, age, disease criteria, details)	AS patients (n=40) ≈ Female 22.5% ≈ Age, years: Etanercept group: 38, Placebo group: 39 ≈ Disease duration, years: Etanercept group: 15, Placebo group: 12 According to the modified New York criteria
Intervention(s)	Etanercept
Intervention(s) characteristics	Responsiveness and discriminative capacity of different measures reflecting disease activity and function, either included in the ASAS DC-ART core set or not, were evaluated comparing etanercept with placebo in patients with ankylosing spondylitis.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue Severity Scale (FSS) Fatigue was a secondary outcome
Effectiveness results	At day-28, mean change of FSS was 0.23 in etanercept group and -0.35 in the placebo group. The results for day 112 were similar. More measures demonstrated low responsiveness when results from all 3 statistical methods were considered ($p<0.50$): Fatigue Severity Scale for day 112.
Safety results	Not stated
Main results	At day 28 of therapy, almost all measures indicated moderate to large responsiveness in the etanercept group (Guyatt 0.60 to 3.11). Some scales of the Short Form 36 (general health, mental component summary, and role emotional), the modified Schober's test, and the Fatigue Severity Scale were not responsive. The results were similar if analyzed at day 112 of therapy. Peripheral joint counts, joint scores, and occiput-to-wall distance could not be evaluated due to a floor effect. In general, the relation between responsiveness and discriminative capacity was strong: Measures that demonstrated high responsiveness also showed high between-group t values.
Follow-up	4 months
Conclusions	Measures included in the ASAS DC-ART core set, except modified Schober's test, have good responsiveness and good discriminatory capacity. Some measures could not be evaluated due to a floor effect.

Weinblatt et al., 2003	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=271) ≈ Female 76.8% ≈ Age 55.5 years ≈ Disease duration 12.3 years 1987 revised criteria of the American College of Rheumatology (ACR)
Intervention(s)	Adalimumab
Intervention(s) characteristics	Patients were randomized to receive placebo or adalimumab at a dosage of 20 mg, 40 mg, or 80 mg subcutaneously every other week as 2 injections of 1.6 ml per injection. Patients were instructed in self-injection techniques.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a secondary outcome
Effectiveness results	After 24 weeks of treatment (LOCF), there were statistically significant differences in the mean increases (improvements) over baseline in FACIT fatigue scale scores in the 40-mg and 80-mg adalimumab dosages plus MTX groups (8.5 and 9.5) vs the placebo plus MTX group (3.0) ($p=0.001$ and $p<0.001$) (data not shown). Similar results were obtained in comparisons of all adalimumab dosage groups combined (8.0) vs placebo (3.0) ($p<0.001$).
Safety results	Adalimumab was safe and well tolerated; comparable numbers of adalimumab-treated patients and placebo-treated patients reported adverse events.
Main results	An American College of Rheumatology criteria for 20% improvement (ACR20) response at week 24 was achieved by a significantly greater proportion of patients in the 20-mg, 40-mg, and 80-mg adalimumab plus MTX groups (47.8%, 67.2%, and 65.8%, respectively) than in the placebo plus MTX group (14.5%) ($p<0.001$). ACR50 response rates with the 20-mg, 40-mg, and 80-mg adalimumab dosages (31.9%, 55.2%, and 42.5%, respectively) were significantly greater than that with placebo (8.1%) ($p=0.003$, $p<0.001$, and $p<0.001$, respectively). The 40-mg and 80-mg doses of adalimumab were associated with an ACR70 response (26.9% and 19.2%, respectively) that was statistically significantly greater than that with placebo (4.8%) ($p<0.001$ and $p=0.020$). Responses were rapid, with the greatest proportion of adalimumab-treated patients achieving an ACR20 response at the first scheduled visit (week 1).
Follow-up	24 weeks
Conclusions	The addition of adalimumab at a dosage of 20 mg, 40 mg, or 80 mg administered subcutaneously every other week to long-term MTX therapy in patients with active RA provided significant, rapid, and sustained improvement in disease activity over 24 weeks compared with MTX plus placebo.

Wells et al., 2007	
Participants characteristics (number, age, disease criteria, details)	RA patients: **ATTAIN** (n=391) and **AIM** (n=652) ≈ Female, %: **ATTAIN=** Abatacept: 77.1, Placebo: 79.7; **AIM=** Abatacept: 77.8, Placebo: 81.7 ≈ Age, years: **ATTAIN=** Abatacept: 53.4, Placebo: 52.7; **AIM=** Abatacept: 51.5, Placebo: 51.4 ≈ Disease duration, years: **ATTAIN=** Abatacept: 12.2, Placebo: 11.4; **AIM=** Abatacept: 8.5, Placebo: 8.9 1987 revised criteria of the American College of Rheumatology (ACR)
Intervention(s)	Abatacept
Intervention(s) characteristics	**The ATTAIN Study:** Eligible and consenting patients were randomized 2:1 to receive abatacept (n=258) or placebo (n=133) on a background of disease modifying antirheumatic drugs (DMARD). **The AIM Study:** Eligible and consenting patients were randomized 2:1 to receive abatacept (n=433) or placebo (n=219) on a background of MTX.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue score: 0–100 (0= no fatigue, 100= complete fatigue) Fatigue was a secondary outcome
Effectiveness results	Negative change scores indicating improvement were found for fatigue, with a 31% reduction in the VAS fatigue score between baseline and final assessment when both studies are combined. In both studies, change of fatigue was -20.71±28.88. Percentage of patients exceeding the MCID of fatigue at 6 months (ATTAIN study) were 58.5% in abatacept group and 37.1% in placebo group (p<0.0001). In addition, Percentage of patients exceeding the MCID of fatigue at 12 months (AIM study) were 69.1% in abatacept group and 51.1% in placebo group (p<0.0001). Mean changes fatigue MCID from baseline to 6 months (ATTAIN study) were -22.3 in abatacept group and -5.3 in placebo group (p<0.0001). In addition, mean changes fatigue MCID from baseline to 12 months (AIM study) were -25.9 in abatacept group and -17.3 in placebo group (p:0.0003).
Safety results	**The ATTAIN Study:** The incidence of adverse events and peri-infusional adverse events was 79.5% and 5.0%, respectively, in the abatacept group and 71.4% and 3.0%, respectively, in the placebo group. The incidence of serious infections was 2.3% in each group. **The AIM Study:** Abatacept-treated patients had a similar incidence of adverse events (87.3% vs 84.0%; difference, 3.3% [CI=2.5 to 9.1%]) and a higher incidence of prespecified serious infections (2.5% vs. 0.9%; difference, 1.6% [CI=0.3 to 3.6%]) and infusion reactions (acute, 8.8% vs. 4.1%; difference, 4.7% [CI=0.9 to 8.4%]; peri-infusional, 24.5% vs. 16.9%; difference, 7.6% [CI=1.2 to 14.0%]) compared with placebo recipients.
Main results	For the 2 trials, consistent patterns of change for activity, fatigue, and sleep and the internal anchors were found with correlations in the range of 0.5, 0.7, and 0.4, respectively. The mean changes for activity, fatigue, and sleep in a narrow range about the MCID of the 3 internal anchors corresponding to the 2 trials were: 3.4 to 4.3 for activity; 6.7 to 17.0 for fatigue; and 4.1 to 7.3 for sleep. Following the Delphi process the MCID determined were 4 for activity, 10 for fatigue, and 6 for sleep.
Follow-up	**The ATTAIN Study:** 6 months **The AIM Study:** 1 year
Conclusions	These MCID for activity limitation, fatigue, and sleep problems can be used in designing clinical trials and providing benchmarks in assessing patient improvement.

Westhovens et al., 2006	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=391) ≈ Female, %: Abatacept group: 77.1, Placebo group: 79.7; ≈ Age, years: Abatacept group: 53.4, Placebo group: 52.7; ≈ Disease duration, years: Abatacept group: 12.2, Placebo group: 11.4 According to the ACR criteria for RA
Intervention(s)	Abatacept
Intervention(s) characteristics	A total of 391 participants were randomized to the abatacept and placebo groups in a 2:1 ratio. Of those who completed the study, fewer abatacept-treated participants than placebo-treated participants discontinued therapy (13.6 and 25.6%, respectively). Patients received a fixed dose of abatacept approximating 10 mg/kg or placebo; patients weighing <60, 60–100 and >100 kg received abatacept 500, 750 and 1000 mg, respectively. Study medication was administered by 30 min intravenous infusion on days 1, 15, 29 and every 28 days thereafter. During the study, 93.8 vs 94.0% of patients in the abatacept vs placebo groups received oral DMARDs; 2.7 vs 2.3% received anakinra. Corticosteroids and NSAIDs were used by approximately 70% of the patients in each group.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue – VAS Fatigue was a secondary outcome
Effectiveness results	Abatacept group had significantly increased fatigue measure compared with similar patients on DMARDS alone (placebo). Some of the results were significantly different between the groups by week eight, including the fatigue scale. The improvement in fatigue score was examined by reviewing the percent of patients who improved by at least half a S.D. by 24 weeks.
Safety results	Not stated
Main results	Treatment group QoL improved significantly more than placebo on the HAQ and fatigue indices, as well as seven of the eight SF-36 scales and SF-36 physical and mental summary scores. Improvement rate was faster for abatacept than for placebo on the QoL measures, and the improvements from abatacept related to normal levels of QoL on many domains.
Follow-up	6 months
Conclusions	Clinically relevant benefits of abatacept over placebo are discussed regarding improving QoL. Importantly, the larger rate of change for abatacept over placebo provides clinicians with a medication that can lead to meaningful changes in a patient's life within a few weeks, even when the patient previously failed anti-TNF therapy.

Yokogawa et al., 2017	
Participants characteristics (number, age, disease criteria, details)	Cutaneous lupus erythematosus (CLE) patients (n=103) ≈ Female, %: Abatacept group: 77.1, Placebo group: 79.7; ≈ Age, years: Abatacept group: 53.4, Placebo group: 52.7; ≈ Disease duration, years: Abatacept group: 12.2, Placebo group: 11.4 According to the ACR criteria for RA
Intervention(s)	Hydroxychloroquine (HCQ)
Intervention(s) characteristics	Patients were randomized 3:1 to receive HCQ or placebo during the 16-week double blind period, and all patients were given HCQ during the following 36-week single-blind period. Patients who participated in the 4-week screening period and met the entry criteria were enrolled and randomized (by computer) to the HCQ group or the placebo group in a 3:1 ratio with a block size of 4. Randomization was stratified according to a CLASI activity score of <9 or ≥ 9 on day 1. For the first 16 weeks, patients randomized to the placebo group received placebo daily (placebo/HCQ group), and those randomized to the HCQ group received HCQ daily (HCQ/HCQ group) (double-blind). At week 16, placebo was switched to HCQ, and both groups received HCQ daily until week 52 (single-blind). Patients were evaluated every 4 weeks and were followed up for 3 weeks after the end of the treatment.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Fatigue – VAS Fatigue was a <u>secondary outcome</u>
Effectiveness results	The decrease in the fatigue score from baseline to week 16 was significant in the HCQ/HCQ group (-1.1; 95% CI=-1.9 to -0.3; p=0.006) but not in the placebo/HCQ group (-0.7; 95% CI=-2.7 to 1.3; p=0.45). The group difference was -0.7 (95% CI=-2.2 to 0.8; p= 0.36).
Safety results	The AEs observed in this study were, in general, commonly associated with antimalarial agents. The occurrence of a “TEAE” and “any serious TEAE” was similar in both groups. No deaths occurred, and no laboratory test values or vital signs showed any clinically significant change during this study in either group. No retinopathy occurred at any point during the study.
Main results	The mean CLASI score at week 16 was significantly improved from baseline in both the HCQ group and the placebo group: mean change -4.6 (95% CI=-6.1 to -3.1; p<0.0001), and mean change -3.2 (95% CI=-5.1 to -1.3; p=0.002), respectively, without between-group difference (p=0.197). The investigator’s global assessment demonstrated a greater proportion of “improved” and “remarkably improved” patients in the HCQ group (51.4% vs 8.7% in the placebo group [p= 0.0002 between groups]). The other secondary end points supported the efficacy of HCQ. Cellulitis, drug eruption, hepatic dysfunction, and Stevens-Johnson syndrome were shown to be serious adverse events related to HCQ use.
Follow-up	55 weeks
Conclusions	The results of this randomized clinical trial support the efficacy and tolerability of HCQ in patients with CLE.

Yount et al., 2007	
Participants characteristics (number, age, disease criteria, details)	RA patients (n=1526) ≈ Female, %: **ARMADA study:** 77, **DE019 study:** 75, **STAR study:** 79 ≈ Age 56 years (median) ≈ Disease duration, years (median): **ARMADA study:** 10, **DE019 study:** 8, **STAR study:** 8
Intervention(s)	Adalimumab
Intervention(s) characteristics	Treatment groups were randomized to placebo plus MTX or 1 of 3 adalimumab arms (20 mg every other week [eow] plus MTX; 40 mg eow plus MTX; or 80 mg eow plus MTX) (22). The DE019 trial enrolled 619 patients who had persistent RA activity after being on MTX for at least 3 months and who were randomized to 1 of 3 treatment arms (placebo plus MTX; adalimumab 20 mg weekly plus MTX; or adalimumab 40 mg eow plus MTX)
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	**ARMADA study:** As early as Week 4, fatigue scores for the adalimumab 80mg (p=0.029) and 40mg (p=0.009) dosage groups were greater (i.e., less fatigue) than those in the placebo group. At Weeks 12 and 24, the fatigue scores in the adalimumab 80mg and 40mg dosage groups were significantly greater than in the placebo group (p<0.05). Fatigue scores for the adalimumab 20mg group were not significantly different from the other dosage groups (including placebo) at any time point. There were significant improvements in fatigue scores from baseline for all treatment arms. At Week 24, fatigue scores for patients had increased from baseline by 11 points (p<0.001) in the adalimumab 80mg group, by 10 points (p<0.001) in the adalimumab 40-mg dosage group, by 8 points (p<0.001) in the adalimumab 20mg dosage group, and, finally, by 6 points (p=0.017) in the placebo group. **DE019 study:** At Weeks 12, 24, and 52, the adalimumab 40mg eow and 20mg weekly dosage groups had significantly greater fatigue scores (i.e., less fatigue) than the placebo group (p<0.001). At Week 52, these fatigue score differences between the adalimumab 40mg eow and 20mg weekly groups relative to the placebo group were 5 and 4.8, respectively, which exceed the minimum clinically important difference of 3–4 points. At Week 24, the 40mg eow and 20mg weekly treatment groups had fatigue scores that were 8 and 9 points greater (i.e., less fatigue) than at baseline, whereas the placebo group had scores 6 points higher. Compared with baseline, Week 52 fatigue scores for the adalimumab 40mg eow and 20mg weekly groups increased by 8 (p<0.001) and 9 (p<0.001) points, respectively, and placebo group fatigue scores were 6 points (p<0.001) greater than baseline. **STAR study:** The adalimumab 40mg dosage arm was 4 points greater (i.e., less fatigue) than placebo both at Week 12 (p<0.001) and at Week 24 (p<0.001). Both treatment arms demonstrated significant improvement in fatigue scores over the course of the study, with the treatment arms improving by 6 points (p<0.001) from baseline to Week 24 and the placebo arm improving an average of 3 points (p<0.001).
Safety results	Not stated
Main results	At baseline in the 3 trials, patients' fatigue ranged from 27.9 fatigue ranged from 27.9-29.7, representing considerable fatigue on the FACIT-F. Fatigue was significantly and consistently reduced in adalimumab-treated patients in the 3 clinical trials. Relative to placebo plus MTX, the adalimumab 40-mg-every-other-week dosage group reported statistically significantly less fatigue at all time points post-baseline. Improvements between adalimumab and placebo ranged from 3-7 points across all 3 trials, with a 3–4-point change representing a minimum clinically important difference.
Follow-up	**ARMADA study:** 24 weeks **DE019 study:** 52 weeks **STAR study:** 24 weeks
Conclusions	Adalimumab treatment was shown to significantly reduce fatigue in patients with moderate to severe RA. Changes in fatigue in all 3 trials were found to be clinically important.

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Participants characteristics (number, age, disease criteria, details)	RA patients (n=216) ≈ Female 85.2 % ≈ Age 48.1 years ≈ Disease duration ranged between group 6.6-9.5 years According to the ACR 1987 revised criteria
Intervention(s)	Tofacitinib
Intervention(s) characteristics	This analysis of data from the Phase 3 study ORAL Sync included Chinese patients randomized 4:4:1:1 to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo→tofacitinib 5 mg twice daily, or placebo→tofacitinib 10 mg twice daily, with csDMARDs. Placebo non-responders switched to tofacitinib at 3 months; the remaining placebo patients switched at 6 months.
Control	Placebo
Outcomes of interest (types and measuring instruments)	Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Fatigue was a primary outcome
Effectiveness results	There were no significant differences between the tofacitinib (5 mg twice daily: 3.3; 10 mg twice daily: 3.6) and placebo (1.5) groups in change from baseline in FACIT-F scores at 3 months. At 6 months, patients receiving tofacitinib 10 mg twice daily demonstrated statistically significant improvement in FACIT-F scores compared with placebo (4.0 vs. 0.6; $p<0.05$). Improvements in FACIT-F scores were maintained in the tofacitinib groups between 6 and 12 months.
Safety results	Not stated
Main results	Overall, 216 patients were included (tofacitinib 5 mg twice daily, n=86; tofacitinib 10 mg twice daily, n=86; placebo→tofacitinib 5 mg twice daily, n = 22; placebo→tofacitinib 10 mg twice daily, n = 22). At month 3, tofacitinib elicited significant improvements in HAQ-DI, Pain, PtGA, PGA and SF-36 Physical Component Summary scores. Improvements were generally maintained through 12 months.
Follow-up	12 months
Conclusions	Tofacitinib 5 and 10 mg twice daily + csDMARDs resulted in improvements in health-related quality of life, physical function, and Pain through 12 months in Chinese patients with RA.