SUPPLEMENTARY APPENDIX 5: ACR/NPF 2018 Psoriatic Arthritis Guideline Evidence Report/Summary

Introduction

Critical outcomes:

- Each table reports the summary of findings (SoF) from randomized trials reporting the critical outcomes. The critical outcomes were chosen at the scoping meeting in September 2016. For nearly all comparisons, the critical outcomes were percentage of patients achieving American College of Rheumatology criteria for 20% improvement (ACR20), Health Assessment Questionnaire Disability Index (HAQ-DI) score, percentage of patients with a 75% reduction in the psoriatic arthritis severity index score (PASI75) and the adverse effect of treatments, including serious infections. If studies did not separately report serious infections, then total infections were included in tables, but not considered a critical outcome. In a few instances, infections were one of the outcomes used in indirect comparisons as described under Evidence Summaries below. A few other critical outcomes were included for individual comparisons.
- It is important to note that serious infections are very rare (infections in general are uncommon/rare), and thus it is quite difficult to achieve a statistically significant difference between groups for this outcome in RCTs powered for efficacy outcomes.
- ACR20 and PASI75 are proportions; The HAQ-DI is typically a continuous outcome but was reported as a binary outcome in some studies (HAQ-DI MCID; % patients who achieved a minimum clinically important difference [0.35 for the HAQ-DI in PsA, but some studies used 0.3 as the minimum change]). Data from studies that reported only continuous HAQ-DI was converted to a binary outcome using the mean change and SD in each group to estimate the proportion of patients achieving a minimal clinically important difference in each group (this method assumes the change scores are normally distributed).
- Not every study identified examined all critical outcomes. Each outcome was analyzed separately.

Therapy groups:

- At our scoping meeting in Sept 2016, we decided upon the following therapy groups:
    - Oral small molecules: this includes methotrexate, sulfasalazine, cyclosporine, leflunomide and apremilast
    - TNF inhibitors (TNFi)
    - IL12/23 inhibitors (IL 12/23i)
    - IL17 inhibitors (IL17i)
    - Abatacept
    - Tofacitinib

Systematic Literature Review

- For most of the outcomes, only randomized controlled trials (RCTs) were included. In some cases, observational studies were examined if relevant RCTs did not exist.

Quality Assessment

- Quality assessment was performed separately for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, which results in one of four possible evidence categories that reflect level of confidence in the effect estimate: high, moderate, low, and very low.
- Study design is the starting point for quality assessment: randomized controlled trials (RCTs) start at high quality and observational studies start at low quality.
- Five factors can lower the quality of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias.
    - Risk of bias refers to limitations in study design or execution (e.g. lack of allocation concealment or blinding).
    - Inconsistency refers to unexplained heterogeneity in results of studies evaluating the same outcome.
    - Indirectness refers to lack of direct comparisons of interventions of interest (e.g. studies comparing drug A vs. placebo and drug B vs. placebo when the comparison of interest is drug A vs. drug B), lack of applicability in the interventions or populations being evaluated, or use of indirect (surrogate) outcome measures.
    - Imprecision refers to uncertainty in the estimate of effect due to very low numbers of patients or events and/or wide 95% confidence intervals that cross a clinical decision threshold (i.e. between recommending and not recommending treatment).
    - Publication bias refers to selective publication of studies that show greater treatment effects (i.e. negative studies are suppressed).
- Three factors can increase the quality of evidence: large effect, dose response, and residual confounding that would reduce the observed treatment effect
    - Large effect refers to an RR >2 or <0.5
    - Dose response gradient refers to an increase in treatment effect or harms observed with increasing medication dose
    - All plausible residual confounding would reduce the demonstrated effect or increase the effect, if no effect was observed
- Quality of evidence can vary from outcome to outcome. The final quality assessment for the PICO question is based on the critical outcome with the lowest quality assessment.

Presentation of effects

- The treatment effects from binary (yes or no) outcomes are presented as relative effects and absolute effects.
- Relative effects capture the difference between intervention and control in relative terms. For example, a 10% event rate in controls

and a 5% event rate in the intervention represents a 50% relative risk reduction [((10- 5)*100)/10]

- The same difference represents a 5% absolute risk reduction (10% - 5% = 5%). In general, for patients, the absolute effect is the most important.

Evidence Summaries including Summary of Findings (= Tables under each PICO question, except some PICO questions for which no evidence was available)

- Indirect comparisons: For PICO questions with a large evidence base, network meta-analysis was used to generate risk ratios (RR) from indirect comparison of different drug classes. Network meta-analysis pools all studies for each comparison of drug A to placebo and studies of drug B to placebo and then divides the pooled odds ratio (OR) for A vs. placebo by the pooled OR for B vs placebo to arrive at an indirect comparison for drug A vs drug B. For PICO questions that had a smaller evidence base (fewer studies), we performed drug-drug comparisons using the Bucher adjusted indirect comparison method, which is conceptually similar to the method used in the network meta-analyses.
- Direct comparisons are situations where trials directly compare drug A to drug B. There are very few trials with direct comparisons among patients with PsA but there are studies where direct comparisons are included for psoriasis and the PASI75 outcome.
- In the tables, when RR is specified, the first drug class (e.g. OSM vs. IL17i) is the reference drug class. Therefore a RR >1 for benefits indicates that the medication listed second is more beneficial; similarly a RR>1 for harms indicates the medication listed second is more harmful.

Interpreting the evidence

- It's important to take into account the information presented specifically as it relates to the question of interest. For example, PICO 22 asks whether switching to an OSM improves outcomes, but the trials reviewed address either adding a new OSM or examine a subgroup of patients in the placebo group with continuation of OSM vs. without continuation. Thus, this evidence is indirect and appropriately gets rated down for indirectness, as shown under the column labeled "indirectness." The quality of evidence takes these sorts of things into account, and is appropriately rated as high, moderate, low or very low. This quality of evidence is key to the voting decisions.

Moving from evidence to recommendations

- In GRADE, recommendations can be either strong or conditional. Generally, strong recommendations are restricted to high or moderate quality evidence. Low quality evidence almost invariably mandates a weak recommendation.
- There are, however, situations in which low quality evidence can lead to strong recommendations. For instance, if there is low quality evidence favoring an intervention but high quality evidence of important harm, the voting panel may make a strong recommendation against the intervention.

Bibliography of included studies

- A complete list of studies included as evidence for this report appears at the end of this document, following PICO 78. Shorter lists of studies included for each PICO question with an evidence base appear at the end of the summaries for each question.

Non-pharmacologic Interventions

PICO 1. In adult patients with active PsA, what are the benefits and harms of exercise compared to no exercise?

Summary: The initial literature searches did not identify any studies that addressed this PICO question. However, a systematic review (SR) and meta-analysis[1] of 14 RCTs in patients with RA found that aerobic exercises were significantly more effective than non-aerobic interventions in improving quality of life (Standardized mean difference [SMD] 0.39, p <0.0001), HAQ score (SMD 0.24, p <0.0009), and VAS pain score (SMD 0.31, p=0.02). Reduction in tender or swollen joint count did not show a statistically significant between-group difference (SMD 0.14, p=0.14). The duration of the trials ranged from 2 to 104 weeks. The average quality of the studies as assessed in the SR was moderate, and the indirectness of the population lowers the overall quality of evidence to low.

An updated literature search in March 2018 identified an additional relevant study, an RCT by Roger-Silva et al.[2] that compared resistance exercise to a waiting-list control in 41 patients with PsA. This trial had not been previously reviewed by the guideline panel. The exercise group showed significant improvement in HAQ-S and BASDAI scores compared to the control group at 12 weeks. This study was small, not blinded and at best, moderate quality, so it does not change the overall quality of evidence.

Quality of evidence across all critical outcomes: Low

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Baillet 2010	SR of 14 RCTs	Study duration ranged from 2 to 104 weeks	Patients with RA	Aerobic exercise interventions vs. non-aerobic exercise or usual care	Aerobic exercise significantly more effective than non-aerobic intervention for the following outcomes: Quality of life: SMD 0.39, 95% CI 0.23 to 0.56, p <0.0001 HAQ score: SMD 0.24, 95% CI 0.10 to 0.38, p <0.0009 VAS pain score: SMD 0.31, 95% CI 0.06 to 0.55, p=0.02 No statistically significant between-group difference for tender or swollen joint count: SMD 0.14, 95% CI -0.05 to 0.33, p=0.14

SMD: standardized mean difference; SR: systematic review

References

1. Baillet A, Zeboulon N, Gossec L, Combescure C, Bodin LA, Juvin R, et al. Efficacy of cardiorespiratory aerobic exercise in rheumatoid arthritis: meta-analysis of randomized controlled trials Arthritis Care & Res 2010; 62(7): 984–992.
2. Roger-Silva D, Natour J. Moreira E, Jennings F. A resistance exercise program improves functional capacity of patients with psoriatic arthritis: a randomized controlled trial. Clin Rheumatol 2018; 37: 389-395.

PICO 2. In adult patients with active PsA, what are the benefits and harms of low impact exercise (e.g., tai chi, yoga, swimming) compared to high impact exercise (e.g., running)?

Summary: The literature searches did not identify any studies that addressed this PICO question. While there are existing systematic reviews of exercise therapy in other arthritis populations (RA, spondyloarthritis), none of these includes studies with a high-impact exercise (running) arm.

Quality of evidence across all critical outcomes: Very low

PICO 3. In adult patients with active PsA with active peripheral arthritis and/or enthesitis, what are the benefits and harms of physical therapy (PT) compared with no PT?

Summary: The literature searches did not identify any studies that directly addressed this PICO question, or any systematic reviews that specifically evaluated PT in patients with other arthritic conditions (e.g. RA). However, PT interventions often overlap with exercise and occupational therapy interventions, so the evidence from PICO 1 and PICO 4 may be applicable to this PICO question. The evidence from both PICO 1 and 4 is noted as having serious risk of bias and serious indirectness, and since none of those interventions were specifically tailored to PT (they overlap with PT), that increases the indirectness to very serious. Therefore, the overall quality of evidence is very low.

Quality of evidence across all critical outcomes: Very low

PICO 4. In adult patients with active PsA with active peripheral arthritis and/or enthesitis, what are the benefits and harms of occupational therapy (OT) compared with no OT?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. Two systematic reviews evaluated OT interventions in patients with RA. Siegel et al.[1] reviewed evidence from earlier SRs and individual RCTs for a range of interventions associated with OT, including various exercise interventions and psychoeducational interventions. Since exercise interventions were covered under PICO 1 and 2, this PICO focuses on psychoeducational interventions. This SR did not report effect sizes but found that psychological interventions generally had at least small effects on pain and function in patients with RA. Knittle et al.[2] performed meta-analyses of 27 RCTs that compared the efficacy of psychological self-regulatory interventions (CBT, patient education, stress management) to controls in patients with RA. These findings appear in the table below; they indicate a small but significant benefit of psychological interventions for the outcomes disability and physical activity at 2 to 14 months follow-up, but pain at follow-up was not significantly different between groups (although immediately post-treatment there was a significant between-group difference in pain reduction favoring the interventions). The average risk of bias in the studies

in these SRs appears to be serious, and since all studies included patients with RA they are limited by serious indirectness. Therefore, the overall quality of evidence is low.

Quality of evidence across all critical outcomes: Low

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Knittle 2010	SR of 27 RCTs	Study duration ranged from 2 weeks to 14 months	Patients with RA	Psychological self-regulatory intervention (CBT, patient education, stress management) vs. control	Outcomes at follow-up (2-14 months post-treatment) Pain: Hedges' g = 0.127 (p=0.069), no significant difference Disability: Hedges' g = 0.145 (p=0.047) Physical activity: Hedges' g = 0.361 (p=0.020)

SMD: standardized mean difference; SR: systematic review

References

1. Siegel S, Tencza M, Apodaca B, Poole J. Effectiveness of occupational therapy interventions for adults with rheumatoid arthritis: a systematic review. Am J Occ Ther. 2017; 71:1-11.
2. Knittle K, Maes S, De Gucht V. Psychological interventions for rheumatoid arthritis: examining the role of self-regulation with a systematic review and meta-analysis of randomized controlled trials. Arth Care & Res. 2010; 62:1460-72.

PICO 5. In adult patients with active PsA who are overweight (e.g., BMI 25 and over), what are the benefits and harms of weight loss compared with no weight loss?

Summary: This PICO question was addressed by direct comparisons in three studies [1-3] but indirect populations in two studies.[2,3] One study compared successful weight loss with unsuccessful weight loss in overweight PsA patients who followed a hypocaloric diet or a free-managed diet. Successful weight loss was defined as ≥ 5% weight loss.[1] Two studies evaluated the effect of weight loss in overweight psoriasis patients following a low-calorie diet.[2,3] Statistically significant differences were reported favoring weight loss over no or unsuccessful weight loss for efficacy outcomes (minimal disease activity [MDA], PASI75).

Quality of evidence across all critical outcomes: Low

Weight loss compared to no or unsuccessful weight loss for overweight PsA patients

Bibliography: PICO 5: Weight loss versus no weight loss for overweight PsA patients.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no or unsuccessful weight loss	**With Weight loss**		**Risk with no or unsuccessful weight loss**	**Risk difference with Weight loss**
MDA, 24 weeks											
126 (1 RCT)	serious [a]	not serious	not serious	serious [e]	none	⨁⨁◯◯ LOW	12/52 (23.1%)	37/74 (50.0%)	**RR 2.17** (1.26 to 3.74) **Favors weight loss**	231 per 1,000 (0.231)	**270 more per 1,000 (0.270)** (60 more to 632 more)
PASI 75, 24 weeks											

Weight loss compared to no or unsuccessful weight loss for overweight PsA patients

Bibliography: PICO 5: Weight loss versus no weight loss for overweight PsA patients.

Quality assessment							Summary of findings				
323 (2 RCTs)	serious [b]	not serious	serious [c]	not serious	none	⊕⊕◯◯ LOW	86/162 (53.1%)	132/161 (82.0%)	**RR 1.67** (1.09 to 2.54) **Favors weight loss**	531 per 1,000 (0.531)	**299 more per 1,000 (0.299)** (212 more to 361 more)[d]

CI: Confidence interval; **MDA**: Minimal disease activity; **RR:** Risk ratio

a. Patients/providers not blinded.

b. Randomization and allocation concealment methods not described; no blinding of patients/providers/assessors (1 study, Al-Mutairi 2014)

c. Population is indirect (psoriasis patients)

d. Absolute risk difference and confidence interval calculated based on the odds ratio.

e. Although the effect size is large, the study does not meet optimal information size.

Notes: Limitations described in 1 study[1] included 20% of patients receiving chronic treatment with oral hypoglycemic agents, possible selection bias resulting in a high prevalence of axial involvement in study population and low baseline PASI scores.

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Di Minno MN, Peluso R, Iervolino S, Russolillo A, Lupoli R, Scarpa R, et al. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor alpha blockers. Ann Rheum Dis. 2014;73(6):1157-1162.
2. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. Am J Clin Nutr. 2008;88(5):1242-1247.
3. Al-Mutairi N, Nour T. The effect of weight reduction on treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial. Expert Opin Biol Ther. 2014;14(6):749-756.

PICO 6. In adult patients with active PsA who smoke, what are the benefits and harms of smoking cessation compared with no smoking cessation?

Summary: The literature searches did not identify any studies that addressed this PICO question. Although specific benefits for PsA or arthritis symptoms are unclear, the general health benefits for smoking cessation are well established. A large RCT in a non-arthritic population found a significant mortality reduction at 14.5 years of follow-up for 5887 patients with asymptomatic airway obstruction who received a smoking cessation intervention compared to a usual care group (hazard ratio [HR] for mortality in usual care group 1.18, 95% CI 1.02 to 1.37).[1] A systematic review of 25 large U.S. and European cohort studies with 503,905 participants ≥60 years of age compared cardiovascular mortality of never smokers, former smokers, and current smokers. With never smokers as the reference group, the individual patient meta-analysis found that former smokers had a lower risk of cardiovascular mortality (HR 1.37, 95% CI 1.25 to 1.49) than current smokers (HR 2.07, 95% CI 1.82 to 2.36).[2] For both studies the only downgrade is for indirectness of the population.

Quality of evidence across all critical outcomes: Moderate

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Anthonisen 2005	RCT	14.5 years	5887 patients with asymptomatic airway obstruction	10-week smoking cessation intervention (with ipratropium or placebo inhaler) vs. usual care	Mortality: Hazard ratio (HR) 1.18 (95% CI 1.02 to 1.37) for usual care group compared to smoking cessation intervention group.
Mons 2015	SR of 25 cohort studies	Mean follow-up across 25 cohort studies ranged from 1.6 to 15.4 years.	503,905 participants ≥60 years of age from 25 cohort studies	Not applicable. An individual patient meta-analysis compared cardiovascular mortality for never smokers, former smokers and current smokers.	With never smokers as the reference group, the individual patient meta-analysis found that former smokers had a lower risk of cardiovascular mortality (HR 1.37, 95% CI 1.25 to 1.49) than current smokers (HR 2.07, 95% CI 1.82 to 2.36).

SR: systematic review

References

1. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE; Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Arthritis Care & Res 2010; 62(7): 984–992. Ann Intern Med. 2005 Feb 15;142(4):233-9.
2. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M,et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. BMJ. 2015 Apr 20;350:h1551.

PICO 7. In adult patients with active PsA, what are the benefits and harms of massage therapy compared with no massage therapy?

Summary: The literature searches did not identify any direct studies that addressed this PICO question. One systematic review, involving seven RCTs with total 352 patients, assessed massage therapy (MT) in patients with OA and RA. The outcomes reported are improved range of motion (ROM), WOMAC functional subscale, grip strength in individuals with hand arthritis, walking function among those with OA of the knee, and adverse events. Five studies (310 participants) provided very low-level evidence that MT is superior to non-active therapy for improving range of motion (ROM). Three RCTs involving 233 participants, provided moderate-quality evidence that MT is superior to non-active therapies in improving WOMAC functional subscales. One study (22 participants provided low-quality evidence that MT was superior to a non-active therapy for improving perceived grip strength in individuals with hand arthritis. Two RCTs with a low risk of bias, and one RCT with a high risk of bias, involving 233 participants, provided moderate quality evidence that MT is superior to a non-active comparator for improving walking function among those with OA of the knee. One study reported significantly faster 50-foot walk times among those receiving MT compared with usual care control participants, whereas another reported decreased time to walk 8 feet in MT recipients compared with participants in a waitlist control group. Adverse effects were reported in two studies: one reported no adverse effects related to the MT intervention, and another reported that one participant experienced an increase in discomfort and subsequently dropped out of the trial.

Quality of evidence across all critical outcomes: Very low

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Nelson L, 2017	Systematic review	Seven RCTs between 1997 and 2015	352 participants with either OA or RA	Massage therapy. The total minutes of massage exposure for the trial period ranged from 120 to 960 mins.	Five studies (310 participants) provided very low-level evidence (downgraded because of risk of bias, imprecision, and inconsistency) that MT is superior to non-active therapy for improving range of motion (ROM). Two trials with a low risk of bias and one trial with a high risk of bias RCT involving 233 participants, provided moderate-quality evidence that MT is superior to nonactive therapies in improving WOMAC functional subscales. One study (22 participants) with a high risk of bias provided low-quality evidence (downgraded because of risk of bias and imprecision) that MT was superior to a nonactive therapy for improving perceived grip strength in individuals with hand arthritis. Two RCTs with a low risk of bias, and one RCT with a high risk of bias, involving 233 participants, provided moderate quality evidence (downgraded because of imprecision) that MT is superior to a nonactive comparator for improving walking function among those with OA of the knee. One study reported significantly faster 50-foot walk times among those receiving MT compared with usual care control participants, whereas another reported decreased time to walk 8 feet in MT recipients compared with participants in a wait list control group. Adverse effects were reported in two studies: one reported no adverse effects related to the MT intervention,

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					and another reported that one participant experienced an increase in discomfort and subsequently dropped out of the trial.

References:

1. Nelson L., Churilla J. Massage Therapy for Pain and Function in Patients with Arthritis. A Systematic Review of Randomized Controlled Trials. Am J Phys Med Rehabil 2017;00:00–00

PICO 8. In adult patients with active PsA, what are the benefits and harms of acupuncture compared with no acupuncture?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. One systematic review addressed acupuncture in older osteoarthritis (OA) patients to measure pain intensity (VAS) and functional mobility.[1] This systematic review included 12 trials (1763 participants) comparing acupuncture to sham acupuncture, no treatment or usual care. Most trials have unclear (64%) or high (9%) risk of bias. Acupuncture use was associated with significant reductions in pain intensity (MD −0.29, 95% CI −0.55 to −0.02, I2 0%, 10 trials, 1699 participants), and functional mobility (standardized MD −0.34, 95% CI −0.55 to −0.14, I2 70%, 9 trials, 1543 participants).

Quality of evidence across all critical outcomes: Very low

Acupuncture Compared to No Acupuncture for Pain Reduction in Osteoarthritis Patients

Bibliography: Acupuncture Compared to No acupuncture for Pain Reduction in Osteoarthritis Patients

Quality Assessment							Summary of Findings				
Number of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With No acupuncture	With Acupuncture		Risk with No acupuncture	Risk difference with Acupuncture
VAS pain											
1699 (10 RCTs)	serious [a]	not serious	very serious [b]	not serious	none	⨁◯◯◯ VERY LOW	829	870	-	-	MD **0.29 lower** (0.55 lower to 0.22 lower)
Functional mobility											
1543 (9 RCTs)	serious [a]	serious [c]	very serious [b]	not serious	none	⨁◯◯◯ VERY LOW	792	751	-	-	SMD **0.34 SD lower** (0.55 lower to 0.14 lower)

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardized mean difference

Explanations

a. Authors of systematic review assigned the risk of bias as serious
b. Indirect population and outcomes
c. High Chi-squared and I-squared values

References:

1. Manyanga T. et al. Pain management with acupuncture in osteoarthritis: a systematic review and meta-analysis. BMC Complementary and Alternative Medicine 2014, 14:312

Pharmacologic Interventions

PICO 9. In adult patients with active PsA who are treatment-naïve, what are the benefits and harms of MTX vs. NSAID?

Summary: This PICO question was addressed directly by one observational study.[1] This retrospective matched study compared NSAIDS with oral MTX in 38 PsA patients. The intervention group were administered methotrexate (MTX) at a maximum weekly dose of 15-20 mg. Controls, who were matched by damage, actively inflamed joints, gender, and disease duration, received NSAIDS. No statistically significant difference was reported for one efficacy outcome (≥40% improvement in actively inflamed joints) or adverse events (GI side effects, hepatic AEs) at 104 weeks, although there was imprecision in the efficacy estimate and very serious imprecision in the adverse event estimates.

Quality of evidence across all critical outcomes: Very low

MTX compared to NSAID for treatment-naive PsA patients

Bibliography: PICO 9: MTX versus NSAID for treatment-naive PsA patients.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With MTX	With NSAID		Risk with MTX	Risk difference with NSAID
> / = 40 % improvement in actively inflamed joints, 104 weeks											
38 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	9/19 (47.4%)	10/19 (52.6%)	**RD 0.05** (-0.26 to 0.37)	474 per 1,000 (0.474)	**50 more per 1,000 (0.050)** (260 fewer to 370 more)
GI side effects (not described), 104 weeks											

MTX compared to NSAID for treatment-naive PsA patients

Bibliography: PICO 9: MTX versus NSAID for treatment-naive PsA patients.

Quality assessment							Summary of findings				
42 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	2/23 (8.7%)	0/19 (0.0%)	**RR 0.24** (0.01 to 4.71)	87 per 1,000	**66 fewer per 1,000 (0.066)**(86 fewer to 323 more)
Hepatic adverse events (not described), 104 weeks											
42 (1 observational study)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	2/23 (8.7%)	0/19 (0.0%)	**RR 0.24** (0.01 to 4.71)	87 per 1,000	**66 fewer per 1,000 (0.066)**(86 fewer to 323 more)

CI: Confidence interval; **RD**: Risk difference

a. Retrospective non-randomized design, no blinding, only 60% of MTX arm at follow-up

b. Small study with few patients and events and wide CI.

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Abu-Shakra M, Gladman DD, Thorne JC, Long J, Gough J, Farewell VT. Longterm methotrexate therapy in psoriatic arthritis: clinical and radiological outcome. J Rheumatol. 1995;22(2):241-245.

PICO 10. In adult patients with active PsA who are treatment-naïve, what are the benefits and harms of an Oral Small Molecule (OSM) vs. TNFi?

Summary: This question was addressed by direct comparisons in 5 RCTs[1-5], and by indirect comparisons in 7 RCTs (in 9 publications).[6-14] Indirect populations (psoriasis patients) were evaluated in 2 studies.[4,5] Table 1 shows a comparison of MTX and infliximab (IFX) combination therapy with MTX monotherapy. Table 2 shows an indirect comparison of MTX and TNFi (adalimumab and etanercept) efficacy outcomes (ACR20, HAQ-DI) from placebo-controlled RCTs. Table 3 shows additional efficacy outcomes and adverse events from RCTs comparing OSMs (MTX or sulfasalazine) to placebo. Table 4 shows additional efficacy outcomes and adverse events from RCTs comparing TNFis (adalimumab or etanercept) to placebo. Lastly, Table 5 shows outcomes from two RCTs comparing TNFi (adalimumab or IFX) with MTX in psoriasis patients[4,5] The results from each table are summarized in the following paragraphs.

One RCT comparing MTX and IFX combination therapy (IFX given in 5 mg/kg infusions at weeks 0, 2, 6 and 14) with MTX monotherapy[1] reported statistically significant differences favoring combination therapy over monotherapy for all efficacy outcomes (ACR20, HAQ-DI, PASI75), but no statistically significant difference for adverse events (pulmonary tuberculosis, upper abdominal pain)(Table 1). Two observational studies comparing MTX with TNFi reported statistically significant differences favoring TNFi for some efficacy outcomes (absolute swollen joint count, modified HAQ-DI, absolute PASI score) but no significant difference for other efficacy outcomes (decrease in swollen joint count, absolute tender joint count, absolute HAQ score) and adverse events (liver toxicity, GI intolerance)(data not shown).[2,3]

One RCT of MTX versus placebo and three RCTs of TNFi (adalimumab or etanercept) vs. placebo reported common outcomes (ACR20, HAQ DI) that could be indirectly compared using the Bucher adjusted indirect comparison method (Table 2). TNFi showed significantly greater benefit than MTX for both outcomes. The MTX trial had a higher percentage of OSM-naïve patients (80%) compared to the TNFi trials (50-60%).

Four RCTs comparing OSM with placebo[6-9] reported no statistically significant difference for all efficacy outcomes (absolute tender joint count, absolute swollen joint count, change in tender joint count). Statistically significant differences favoring placebo were reported for one adverse event (GI intolerance). However, no statistically significant difference was reported between OSM and placebo for another adverse event (liver toxicity). A subgroup analyses by drug indicated a statistically significant difference favoring placebo over methotrexate for liver toxicity, but no statistically significant difference between sulfasalazine and placebo (Table 3).

Three RCTs (5 publications)[10-14] comparing TNFi with placebo reported statistically significant differences favoring TNFi over placebo for all efficacy outcomes (ACR20, HAQ-DI, PASI75), but no statistically significant difference for all adverse events (serious AEs, serious infections, upper respiratory tract infections)(Table 4).

Lastly, two RCTs comparing TNFi (adalimumab or IFX) with MTX in psoriasis patients[4,5] reported a statistically significant difference favoring TNFi over MTX for one skin outcome (measured by PASI75), but no statistically significant difference for two adverse outcomes (liver function test abnormality, serious infection)(Table 5).

Quality of evidence across all critical outcomes: Low

Table 1. MTX/IFX compared to MTX for treatment-naive PsA patients
Bibliography: PICO 10: OSM versus TNFi for treatment-naive PsA patients.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With MTX	With MTX/IFX		Risk with MTX	Risk difference with MTX/IFX
ACR20 response, 16 weeks											
99 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	32/48 (66.7%)	44/51 (86.3%)	**RR 1.29** (1.03 to 1.63) **Favors MTX/IFX**	667 per 1,000 (0.667)	**196 more per 1,000 (0.196)** (32 more to 278 more)[d]
HAQ-DI[b], 16 weeks											
110 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	33/54 (61.1%)	45/56 (80.4%)	**RR 1.31** (1.03 to 1.69) **Favors MTX/IFX**	611 per 1,000 (0.611)	**192 more per 1,000 (0.192)** (24 more to 295 more)[d]
PASI75, 16 weeks											

Table 1. MTX/IFX compared to MTX for treatment-naive PsA patients

Bibliography: PICO 10: OSM versus TNFi for treatment-naive PsA patients.

Quality assessment							Summary of findings				
69 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	19/35 (54.3%)	33/34 (97.1%)	**RR 1.79** (1.31 to 2.44) **Favors MTX/IFX**	543 per 1,000 (0.543)	**428 more per 1,000 (0.428)** (259 more to 453 more)[d]
Pulmonary tuberculosis[e]											
111 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	1/57 (1.8%) MTX/IFX	0/54 (0.0%) MTX	**RR 0.35** (0.01 to 8.45)	18 per 1,000 MTX/IFX	**12 fewer per 1,000 with MTX (0.012)** (18 fewer to 134 more)
Upper abdominal pain											
111 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	3/54 (5.6%)	0/57 (0.0%)	**RR 0.14** (0.01 to 2.56)	56 per 1,000 (0.056)	**48 fewer per 1,000 (0.048)** (55 fewer to 143 more)

CI: Confidence interval; **RD**: Risk difference; **RR:** Risk ratio

a. Unclear randomization and allocation concealment methods, no blinding

b. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

c. Single small study with very few events

d. Absolute risk difference and confidence interval calculated based on the odds ratio.

e. For pulmonary tuberculosis there were zero events in the MTX group, so we used MTX/IFX as the denominator in order to calculate the RR. So in this comparison “12 fewer per 1,000” means 12 fewer events in the MTX group compared to MTX/IFX.

Table 2. MTX compared to TNFi for treatment-naive PsA patients

Bibliography: PICO 10: OSM versus TNFi for treatment-naive PsA patients.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**			**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With TNFi	**With MTX**		**Risk with TNFi**	**Risk difference with MTX**
ACR20 response, Bucher adjusted indirect comparison											
799 (4 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	TNFi	MTX	**OR[b] 0.24** (0.07 to 0.72) **Favors TNFi**	596 per 1,000 (0.596)	**335 fewer per 1,000 (0.335)** (502 fewer to 58 fewer)[d]
HAQ-DI[c], Bucher adjusted indirect comparison											
799 (4 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	TNFi	MTX	**RR 0.63** (0.42 to 0.95) **Favors TNFi**	596 per 1,000 (0.596)	**221 fewer per 1,000 (0.221)** (346 fewer to 30 fewer)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison of placebo-controlled trials
b. Study of MTX reported finding as OR, so indirect comparison had to use OR.
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).
d. Absolute risk difference and confidence interval calculated based on the odds ratio.

Table 3. OSM compared to placebo for treatment-naive PsA patients

Bibliography: PICO 10: OSM versus TNFi for treatment-naive PsA patients.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With OSM**		**Risk with placebo**	**Risk difference with OSM**
Absolute tender joint count (8-12 weeks)											
245 (2 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	126	119	-	-	MD **3.31 lower** (9.11 lower to 2.49 higher)
Absolute swollen joint count (8-12 weeks)											
245 (2 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	126	119	-	-	MD **1.36 lower** (5.47 lower to 2.74 higher)
Change in tender joint count (53 joints, week 24)											
108 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	59	49	-	-	MD **0.8 lower** (2.17 lower to 0.57 higher)
GI intolerance (nausea, vomiting, abdominal pain, diarrhea)											

Table 3. OSM compared to placebo for treatment-naive PsA patients

Bibliography: PICO 10: OSM versus TNFi for treatment-naive PsA patients.

Quality assessment							Summary of findings				
392 (4 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	30/205 (14.6%)	67/187 (35.8%)	**RR 2.38** (1.64 to 3.46) **Favors placebo**	146 per 1,000 (0.146)	**202 more per 1,000 (0.202)** (94 more to 360 more)
Liver toxicity[c] - Methotrexate vs placebo											
221 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	2/112 (1.8%)	12/109 (11.0%)	**RD 0.09** (0.03 to 0.16) **Favors placebo**	18 per 1,000 (0.018)	**90 more per 1,000 (0.090)** (30 more to 160 more)
Liver toxicity[d] - Sulfasalazine vs placebo											
117 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	1/64 (1.6%)	0/53 (0.0%)	**RR 0.40** (0.02 to 9.65)	16 per 1,000 (0.016)	**9 fewer per 1,000 (0.009)** (15 fewer to 135 more)

CI: Confidence interval; **MD:** Mean difference; **RD**: Risk difference; **RR:** Risk ratio

a. Indirect comparison

b. Wide 95% CI crosses line of no difference

c. Abnormal liver function tests, but study did not define cutoff.

d. Increased ASAT and ALAT (x 3 compared to baseline) after 1 month. No concomitant NSAID.

Table 4. TNFi compared to Placebo for treatment-naive PsA patients

Bibliography: PICO 10: OSM versus TNFi for treatment-naive PsA patients.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With TNFi		Risk with Placebo	Risk difference with TNFi
PASI 75											
326 (3 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	11/161 (6.8%)	80/165 (48.5%)	**RD 0.37** (0.09 to 0.65) **Favors TNFi**	68 per 1,000 (0.068)	**370 more per 1,000 (0.370)** (90 more to 650 more)
Serious Infections											
518 (2 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	2/266 (0.8%)	1/252 (0.4%)	**RD -0.004** (-0.02 to 0.01)	8 per 1,000 (0.008)	**4 fewer per 1,000 (0.004)** (20 fewer to 10 more)
Upper respiratory tract infection 12 weeks											
60 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	17/30 (56.7%)	17/30 (56.7%)	**RR 1.00** (0.64 to 1.56)	567 per 1,000 (0.567)	**0 fewer per 1,000** (204 fewer to 317 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison

b. Wide CIs

Table 5. TNFi compared to OSM for treatment-naive psoriasis patients

Bibliography: PICO 10: OSM versus TNFi for treatment-naive PsA patients.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With OSM (Psoriasis)	With TNFi		Risk with OSM (Psoriasis)	Risk difference with TNFi
PASI-75, 16 weeks											
1086 (2 RCTs)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	129/325 (39.7%)	594/761 (78.1%)	**RR 1.98** (1.66 to 2.36) **Favors TNFi**	397 per 1,000 (0.397)	**389 more per 1,000 (0.389)** (262 more to 540 more)
Liver function test abnormality[c] - Infliximab vs. MTX											
860 (1 RCT)	serious [d]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	3/211 (1.4%)	14/649 (2.2%)	**RD 0.01** (-0.01 to 0.03)	14 per 1,000 (0.014)	**10 more per 1,000 (0.010)** (10 fewer to 30 more)
Liver function test abnormality[e] - Adalimumab vs. MTX											
217 (1 RCT)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	10/110 (9.1%)	2/107 (1.9%)	**RR 0.21** (0.05 to 0.92) **Favors ADA**	91 per 1,000 (0.091)	**72 fewer per 1,000 (0.072)** (86 fewer to 7 fewer)

Table 5. TNFi compared to OSM for treatment-naive psoriasis patients

Bibliography: PICO 10: OSM versus TNFi for treatment-naive PsA patients.

Quality assessment							Summary of findings				
Serious Infection											
1077 (2 RCTs)	serious [a]	not serious	serious [b]	not serious	none	⊕⊕◯◯ LOW	4/321 (1.2%)	10/756 (1.3%)	**RD 0.001** (-0.01 to 0.02)	12 per 1,000 (0.012)	**1 more per 1,000 (0.001)** (10 fewer to 20 more)

CI: Confidence interval; **RD**: Risk difference; **RR:** Risk ratio

a. 1 RCT (Barker 2011) open label, ITT conducted

b. Indirect population (Psoriasis patients)

c. Elevated liver enzymes (study did not report cutoffs for abnormal test results)

d. Open label, ITT conducted

e. Alanine aminotransferase > 2.5 times the upper normal limit (ULN), aspartate aminotransferase > 2.5 times the ULN, total bilirubin >1.5 times the ULN, or ỹ- Gamma-Glutamyltransferase elevation

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 11. In adult patients with active PsA who are treatment-naïve, what are the benefits and harms of an OSM vs. IL12/23?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 12. In adult patients with active PsA who are treatment-naïve, what are the benefits and harms of an OSM vs. IL17i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 13. In adult patients with active PsA who are treatment-naïve, what are the benefits and harms of a TNFi vs. IL12/23i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 14. In adult patients with active PsA who are treatment-naïve, what are the benefits and harms of TNFi vs. IL17i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 15. In adult patients with active PsA who are treatment-naïve, what are the benefits and harms of IL12/23i vs. IL17i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 16. In adult patients with active PsA despite treatment with OSM, what are the benefits and harms of switching to TNFi compared to switching to IL12/23i?

Summary: Thirteen placebo-controlled RCTs (16 publications) indirectly addressed this PICO question. Nine studies (12 publications) compared TNFi versus placebo in PsA patients.[1-12] Three studies compared IL 12/23 (ustekinumab) with placebo in PsA patients.[13-15] Lastly, one study compared etanercept with ustekinumab in psoriasis patients.[16] Statistically significant differences favoring TNFi over placebo and ustekinumab over placebo were reported for all efficacy outcomes (ACR20, HAQ-DI, PASI-75, data not shown). No statistically significant differences with placebo occurred for any adverse events (see Table 3 for serious infections). In addition, both TNFi-naïve and TNFi-exposed patients responded similarly to TNFi and ustekinumab compared to placebo (data not shown).

A network meta-analysis (method described in the Introduction under Evidence Summaries) was performed based on indirect comparisons of the placebo-controlled RCTs noted above (Table 1). Due to substantial heterogeneity in findings among different TNFis for ACR 20 and PASI75, the individual drugs were separated in the network meta-analysis. Of individual TNFIs, golimumab (GOL) and infliximab were associated with significantly greater proportions of patients who achieved ACR20 compared to ustekinumab, while only infliximab was associated with significantly greater proportions of patients who achieved PASI75 compared to ustekinumab (see table below). The relative risk for golimumab was elevated in part due to a low placebo event rate (8.8%) in the GO-REVEAL trial compared to the ustekinumab trials (average 20.5%). Other individual TNFis did not show superiority over ustekinumab for these outcomes, but imprecision due to wide confidence intervals that overlapped the line of no difference means that the findings were inconclusive (data not shown). The findings for HAQ DI (proportion of patients who achieved a minimum important change) were also inconclusive between TNFIs and ustekinumab due to a wide CI that overlapped the line of no difference. Infection rates (the only relevant adverse event that could be compared between drug classes) did not differ significantly between TNFis and ustekinumab (this outcome was compared using the Bucher adjusted indirect method, see description in the Introduction to this report). For illustrative purposes the network meta-analyses for ACR20 and HAQ-DI are diagrammed in Figures 1 and 2, respectively. An updated literature search in March 2018 identified one additional RCT showing superiority of golimumab over placebo[19]. This trial had not been previously reviewed by the panel, but it was moderate quality (due to indirectness) and the results did not change the overall findings or the overall quality of evidence.

One trial of psoriasis patients found statistically significant differences favoring ustekinumab over etanercept for one efficacy outcome (PASI75), but no significant differences were reported for serious infections (Table 2).[16] However, the event rate for serious infections was so low that the finding is inconclusive. The PASI75 finding was also supported by a published network meta-analysis of RCTs of patients with psoriasis.[17] In this analysis ustekinumab showed superiority over etanercept for PASI75 (OR 1.94, 95% CI 1.31 to 3.01) and did not differ significantly from adalimumab (OR 1.44, 95% CI 0.82 to 2.58), although the latter finding is inconclusive due to imprecision in the CI. However, Infliximab showed superiority over ustekinumab in this network meta-analysis (OR 3.92, 95% CI 1.83 to 9.06), which is consistent with the findings of our

independently performed network meta-analysis of PsA RCTs. A published meta-analysis of psoriasis RCTs found no significant difference between TNFi versus placebo and IL12/23i versus placebo in rates of major adverse cardiovascular events.[18]

Quality of evidence across all critical outcomes: Moderate

Table 1. TNFi compared to IL12/23i for patients with active PsA despite OSM
Bibliography: PICO 16: TNFi compared to IL12/23i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**			**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With IL12/23i	**With TNFi**		**Risk with IL12/23i**	**Risk difference with TNFi**
ACR20, 12-24 weeks, network meta-analysis											
1332 (4 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL12/23i	GOL	**RR 2.44** (1.17 to 5.13) **Favors GOL**	449 per 1,000 (0.449)	**289 more per 1000 (0.289)**(44 more to 441 more)[c]
1431 (6 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL12/23i	IFX	**RR 3.19** (1.87 to 5.46) **Favors IFX**	449 per 1,000	**417 more per 1000 (0.417)**(159 more to 515 more)[c]
HAQ-DI[d], 12-24 weeks, network meta-analysis											

Table 1. TNFi compared to IL12/23i for patients with active PsA despite OSM

Bibliography: PICO 16: TNFi compared to IL12/23i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
2477 (10 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL12/23i	TNFi	**RR 0.99** (0.76 to 1.30) **No difference**	441 per 1,000	**4 fewer per 1000 (0.004)** (106 fewer to 132 more)
PASI 75, 12-24 weeks, network meta-analysis											
1023 (5 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL12/23i	IFX	**RR 3.34** (1.1 to 10.2) **Favors IFX**	569 per 1,000 (0.569)	**306 more per 1000 (0.306)** (66 more to 397 more) [c]
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
1025 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	ADA	**RR 0.56** (0.26 to 1.22)	211 per 1,000	**93 fewer per 1000 (0.093)** (156 fewer to 46 more)
1199 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	CZP	**RR 1.19** (0.80 to 1.76)	211 per 1,000	**40 more per 1000 (0.040)** (42 fewer to 160 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. Absolute risk differences calculated from odds ratios obtained using the Bucher method.
d. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

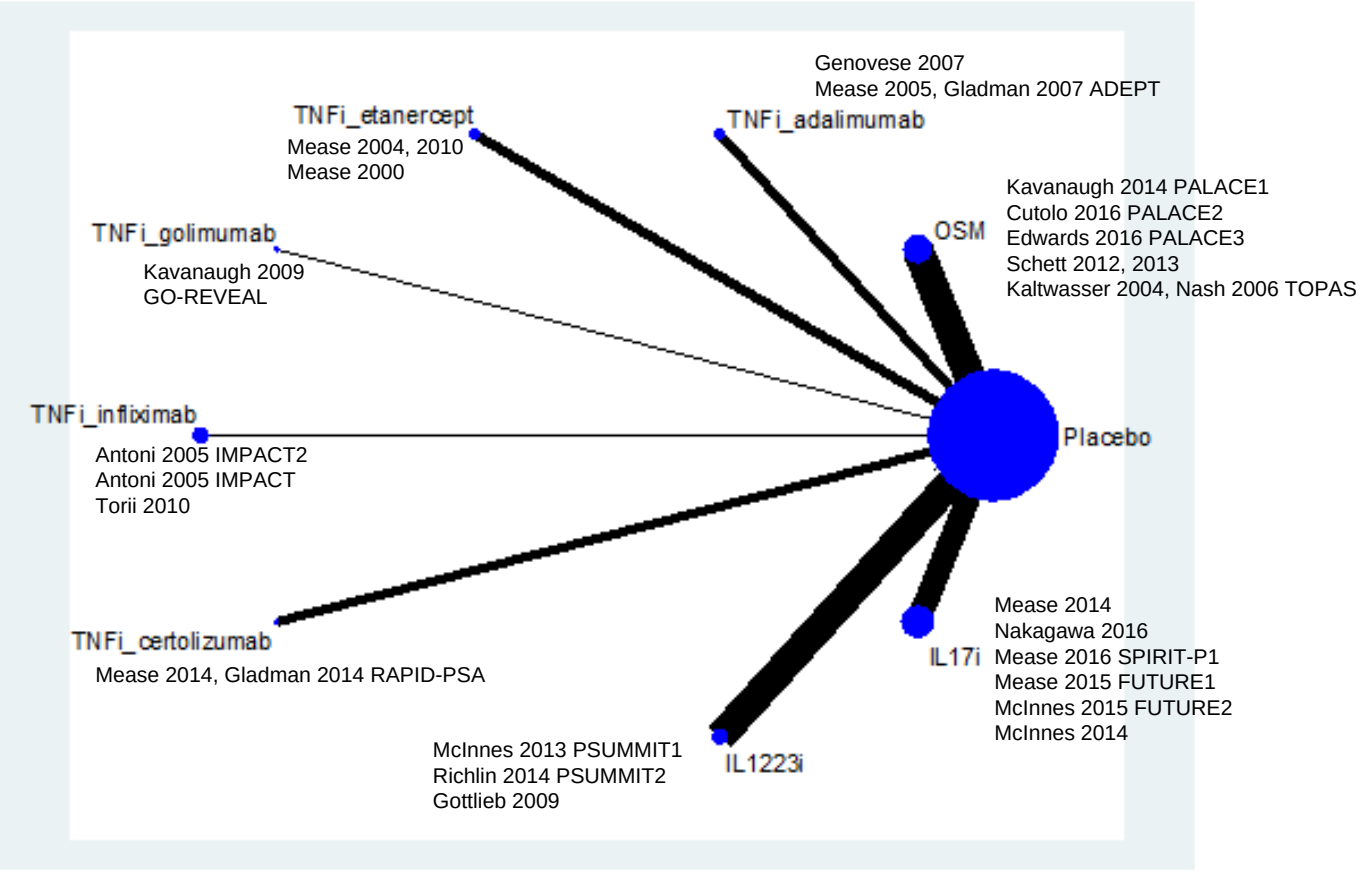

Figure 1. Network meta-analysis for ACR20. Node (blue circle) size and line thickness varies based on number of studies and patients in each comparison. The largest circle represents the placebo node (because all RCTs had a placebo control) and the branching lines connect to smaller nodes representing each of the treatments. Due to substantial heterogeneity within the TNFi class the individual TNFi drugs were analyzed separately and compared to the other drug classes (OSM, IL12/23i, and IL17i). The figure also identifies the specific trials that provided data for each treatment node.

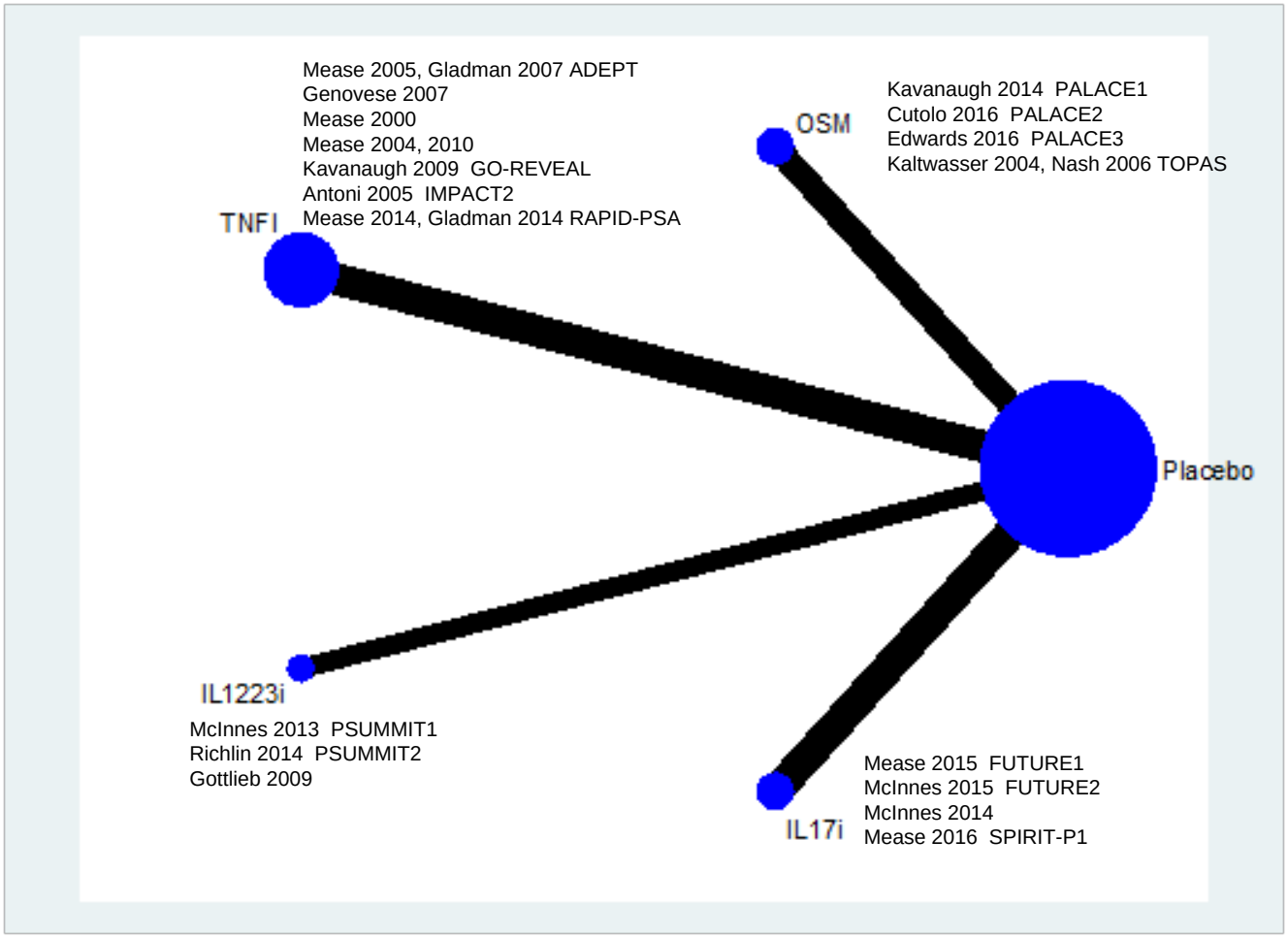

Figure 2. Network meta-analysis for HAQ-DI. Since there was no substantial heterogeneity within each drug class, a straight drug class comparison was performed for this outcome.

Table 2. TNFi compared to IL12/23i for patients with Psoriasis despite OSM

Bibliography: PICO 16: TNFi versus IL12/23i for PsA patients who failed OSM.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With TNFi (ETN)	**With IL12/23i**		**Risk with TNFi**	**Risk difference with IL12/23i**
PASI-75 at 12 weeks											
903 (1 RCT)	not serious	not serious	serious[a]	not serious	none	⨁⨁⨁◯ MODERATE	197/347 (56.8%)	397/556 (71.4%)	**RR 1.26** (1.13 to 1.40) **Favors IL12/23i**	568 per 1,000 (0.568)	**148 more per 1,000 (0.148)** (74 more to 227 more)
Serious Infection											
903 (1 RCT)	not serious	not serious	serious[a]	not serious	none	⨁⨁⨁◯ MODERATE	1/347 (0.3%)	4/556 (0.7%)	**RD 0.004** (-0.002 to 0.010)	3 per 1,000	**4 more per 1,000 (0.004)** (2 fewer to 10 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect population (psoriasis)

Table 3. TNFi or IL12/23i compared to placebo for PICO 16: Adverse events

Bibliography: PICO 16: TNFi versus IL 12/23i for PsA patients who failed OSM.

Quality assessment	Summary of findings

Table 3. TNFi or IL12/23i compared to placebo for PICO 16: Adverse events

Bibliography: PICO 16: TNFi versus IL 12/23i for PsA patients who failed OSM.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With drug**		**Risk with placebo**	**Risk difference with TNFi or IL12/23i**
Serious infection – TNFi vs. placebo											
1151 (5 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	8/564 (1.4%)	4/587 (0.7%)	**RR 0.54** (0.17 to 1.77) **No difference**	14 per 1,000 (0.014)	**6 fewer per 1,000 (0.006)** (12 fewer to 11 more)
Serious infection – Ustekinumab vs. placebo											
925 (2 RCTs)	not serious	serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	2/309 (0.6%)	4/616 (0.6%)	**RR 0.84** (0.20 to 3.50) **No difference**	6 per 1,000 (0.006)	**1 fewer per 1,000** (5 fewer to 15 more)

CI: Confidence interval; **RR:** Risk ratio

a. Comparison to placebo

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 17. In adult patients with active PsA despite treatment with OSM, what are the benefits and harms of switching to TNFi compared to switching to IL17i?

Summary. This question was addressed indirectly by 19 double-blind RCTs (22 publications). Two reports of the same study directly compared IL17i (secukinumab) to TNFi (etanercept) among patients with psoriasis; one study specifically reported data only for a subgroup of patients with PsA[1], and one report of outcomes for the whole population (patients with psoriasis)[2]. Nine studies (12 publications) involving PsA patients compared TNFis to placebo.[3-14] One study compared ixekizumab to placebo,[15] three studies compared secukinumab to placebo,[16-18] and three studies compared brodalumab to placebo[19-21] (note: brodalumab is currently FDA-approved for psoriasis but not PsA). Three studies (2 publications) compared secukinumab 300mg to secukinumab 150mg. All drugs showed statistically significant improvements in ACR20, PASI75, and HAQ-DI over placebo, while no significant difference was found for infections, but with high imprecision in the effect estimate. Subgroup analysis of previous TNFi exposure did not find differences between exposed and unexposed subgroups, but no studies specified whether TNFi experienced patients had TNFi treatment failure. In the study comparing secukinumab to etanercept, PASI75 was superior in the secukinumab group with statistically significant results (Table 1). A study of patients with psoriasis similarly found that ixekizumab was superior to etanercept for increasing PASI-75 (Table 2).[22] In studies comparing ACR20, PASI-75 and HAQ-DI for patients dosed with 300mg vs. 150mg of secukinumab, all outcomes showed no significant difference between the two doses of secukinumab, with direction of effect slightly favoring 300 mg (RR 1.06-1.15) but slight imprecision in the CIs (data not shown).

A network meta-analysis was performed to indirectly compare TNFis vs IL17is using the placebo-controlled RCTs noted above (see Table 1). Due to substantial heterogeneity in findings among different TNFis for ACR20, the individual TNFis were separated in the network meta-analysis. Of individual TNFis, only golimumab and infliximab were associated with a significantly higher proportion of patients who achieved ACR20 when compared to patients who received IL17is. The remaining TNFis did not show a significant difference compared to IL17is for ACR20, although all of these findings were inconclusive due to imprecise CIs that overlapped with the line of no difference (data not shown). For HAQ-DI minimum improvement, there was no substantial heterogeneity among different TNFis so a straight drug class comparison was performed. No significant difference between TNFis and IL17is was identified for this outcome, although the findings were inconclusive due to imprecision in the effect estimate. For PASI-75, although there was some heterogeneity among TNFis, none showed a significant difference with IL17is, so a straight drug class comparison was performed (there was also some heterogeneity among trials of secukinumab). The overall comparison found no significant between-class difference, but the findings were inconclusive due to imprecision in the effect estimate. Bucher adjusted indirect comparisons were performed for the outcome of infections (the only relevant adverse event reported by both sets of drug class trials). The two TNFi trials (one adalimumab, one certolizumab) showed heterogeneity and differences in effect direction, so they were separately compared to two trials of secukinumab that reported this outcome. Both comparisons found no significant difference but were inconclusive due to imprecision in the effect estimates. Six TNFi RCTs and 3 IL17i RCTs reported serious infections and found no significant difference between drug and placebo groups, although the finding was imprecise for IL17i due to a wide 95% CI (Table 3). A published meta-analysis of psoriasis RCTs found no significant difference between TNFi versus placebo and IL17i versus placebo in rates of major adverse cardiovascular events.[23] An updated

literature search in March 2018 identified one additional RCT showing superiority of golimumab over placebo[24]. This trial had not been previously reviewed by the panel, but it was moderate quality (due to indirectness) and the results did not change the overall findings or the overall quality of evidence.

Quality of evidence across all critical outcomes: Low

Table 1. TNFi compared to IL17i for patients with active PsA despite OSM
Bibliography: PICO 17: TNFi compared to IL17i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							IL17i	TNFi		Risk with IL17i	Risk difference with TNFi
ACR20, 12-24 weeks, network meta-analysis											
1229 (7 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL17i	GOL	**RR 2.21** (1.1 to 4.48) **Favors GOL**	503 per 1,000 (0.503)	**213 more per 1000 (0.213)** (33 more to 344 more)[e]
1328 (9 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL17i	IFX	**RR 2.89** (1.79 to 4.67) **Favors IFX**	503 per 1,000 (0.503)	**351 more per 1000 (0.351)** (80 more to 458 more)[e]
HAQ-DI[f], 12-24 weeks, network meta-analysis											

Table 1. TNFi compared to IL17i for patients with active PsA despite OSM

Bibliography: PICO 17: TNFi compared to IL17i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
2258 (11 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	TNFi	**RR 1.28** (0.97 to 1.68)	556 per 1,000 (0.556)	**156 more per 1000 (0.156)** (17 less to 378 more)
PASI 75, 12-24 weeks, network meta-analysis											
1837 (14 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	TNFi	**OR 0.82** (0.29 to 2.34)	643 per 1,000 (0.643)	**47 fewer per 1000 (0.047)** (300 fewer to 165 more)[e]
PASI 75, 12-24 weeks, direct comparison (secukinumab versus etanercept)											
1 RCT (143 patients)	Serious[c]	Not serious	Serious[d]	Not serious	None	⨁⨁◯◯ LOW	IL17i (SEC)	ETN	**RR 0.59** (0.40 to 0.88) **Favors SEC**	657 per 1,000 (0.657)	**270 fewer per 1,000 (0.270)** (79 fewer to 394 fewer)
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
702 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	ADA	**RR 0.45** (0.21 to 1.01)	313 per 1,000 (0.313)	**172 fewer per 1000 (0.172)** (247 fewer to 0 more)

Table 1. TNFi compared to IL17i for patients with active PsA despite OSM

Bibliography: PICO 17: TNFi compared to IL17i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
876 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	CZP	**RR 0.94** (0.59 to 1.50)	313 per 1,000 (0.313)	**19 fewer per 1000 (0.019)** (128 fewer to 157 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide CI that is close to or crosses line of no difference
c. PsA diagnosis based on patient records; PsA activity not measured within the study.
d. Only 63% of patients had prior OSM exposure
e. Absolute risk differences calculated from odds ratios obtained using the Bucher method.
f. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

Table 2. TNFi compared to IL17i for patients with psoriasis despite OSM

Bibliography: PICO 17 - TNFi compared to IL17i for patients with active PsA despite OSM.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With TNFi (ETN)	**With IL17 (IXE)**		**Risk with TNFi**	**Risk difference with IL17i**
PASI-75 at week 12											

Table 2. TNFi compared to IL17i for patients with psoriasis despite OSM

Bibliography: PICO 17 - TNFi compared to IL17i for patients with active PsA despite OSM.

Quality assessment							Summary of findings				
1476 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	353/740 (47.7%)	651/736 (88.5%)	**RR 1.85** (1.71 to 2.01) **Favors IL17 (IXE)**	477 per 1,000 (0.477)	**405 more per 1,000 (0.405)** (339 more to 482 more)
Infection											
1473 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	159/739 (21.5%)	190/734 (25.9%)	**RR 1.20** (1.00 to 1.45)	215 per 1,000 (0.215)	**43 more per 1,000 (0.043)** (0 fewer to 97 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect population (psoriasis)

Table 3. TNFi or IL17i compared to placebo for PICO 17: Adverse events

Bibliography: PICO 17: TNFi versus IL17i for PsA patients who failed OSM.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With TNFi or IL17i**		**Risk with placebo**	**Risk difference with TNFi or IL17i**
Serious infection – TNFi vs. placebo											

Table 3. TNFi or IL17i compared to placebo for PICO 17: Adverse events

Bibliography: PICO 17: TNFi versus IL17i for PsA patients who failed OSM.

Quality assessment							Summary of findings				
1151 (5 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	8/564 (1.4%)	4/587 (0.7%)	**RR 0.54** (0.17 to 1.77) **No difference**	14 per 1,000 (0.014)	**6 fewer per 1,000 (0.006)** (12 fewer to 11 more)
Serious infection – IL17i vs. placebo											
1189 (3 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/406 (1.2%)	18/685 (2.6%)	**RR 1.79** (0.75 to 4.30)	12 per 1,000 (0.012)	**9 more per 1,000 (0.009)** (3 fewer to 52 more)

CI: Confidence interval; **RR:** Risk ratio

a. Comparison to placebo

b. Wide 95% CI that crosses line of no effect

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 18. In adult patients with active PsA despite treatment with OSM, what are the benefits and harms of switching to IL12/23i compared to switching to IL17i?

Summary: This PICO question was addressed indirectly by 16 double-blind RCTs (13 publications). Three studies (2 publications) involving psoriasis patients compared IL12/23i (ustekinumab) to IL17i.[1,2] Thirteen studies (11 publications) involving PsA patients or psoriasis patients compared either IL12/23i or IL17i to placebo.[3-13] All drugs showed statistically significant improvements in ACR20, PASI-75, and HAQ-DI over placebo (data not shown).

A network meta-analysis was performed to indirectly compare IL12/23i vs IL17is using the placebo-controlled RCTs noted above. The meta-analysis showed no significant between-class differences for the outcomes ACR20, HAQ-DI and PASI-75, but there was imprecision in all effect sizes due to wide CIs (see Table 1). A Bucher adjusted indirect comparison similarly found no significant between-class difference in infection rates, again with imprecision due to a wide CI.

Studies of patients with psoriasis found no significant difference in PASI-75 when comparing ustekinumab to brodalumab. The psoriasis study comparing ustekinumab to secukinumab reported that PASI-75 was superior in the secukinumab group and there was no significant difference in infection rates between the two groups (Table 2).

Serious infections for drug vs. placebo groups appear in Table 3. Neither IL12/23i nor IL17i showed significantly different serious infection rates compared to placebo groups, but the findings were imprecise for IL17i due to a wide 95% confidence interval.

Quality of evidence across all critical outcomes: Moderate

Table 1. IL12/23i compared to IL17i for patients with active PsA despite OSM
Bibliography: PICO 18: IL12/23i compared to IL17i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							IL12/23i	IL17i		Risk with IL12/23i	Risk difference with IL17i
ACR20, 12-24 weeks, network meta-analysis											

Table 1. IL12/23i compared to IL17i for patients with active PsA despite OSM

Bibliography: PICO 18: IL12/23i compared to IL17i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
2043 (9 RCTs)	Not serious	Not serious	Not serious [a]	Serious[b]	None	⊕⊕⊕◯ MODERATE	**IL12/23i**	**IL17i**	**RR 1.1** (0.69 to 1.77)	449 per 1,000 (0.449)	**45 more per 1000 (0.045)** (139 fewer to 346 more)
HAQ-DI[c], 12-24 weeks, network meta-analysis											
1913 (7 RCTs)	Not serious	Not serious	Not serious [a]	Serious[b]	None	⊕⊕⊕◯ MODERATE	**IL12/23i**	**IL17i**	**RR 0.81** (0.58 to 1.13)	441 per 1,000 (0.441)	**84 fewer per 1000 (0.084)** (185 fewer to 57 more)
PASI 75, 12-24 weeks, network meta-analysis											
1630 (9 RCTs)	Not serious	Not serious	Not serious [a]	Serious[b]	None	⊕⊕⊕◯ MODERATE	**IL12/23i**	**IL17i**	**RR 1.20** (0.46 to 3.12)	569 per 1,000 (0.569)	**112 more per 1000 (0.112)** (92 less to 265 more)[d]
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
1527 (4 RCTs)	Not serious	Not serious	Not serious [a]	Serious[b]	None	⊕⊕⊕◯ MODERATE	**IL12/23i**	**IL17i**	**RR 1.26** (0.81 to 1.97)	211 per 1,000 (0.211)	**55 more per 1000 (0.112)** (40 less to 205 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure, but patient characteristics and prior drug exposure are similar between drug classes.
b. Wide 95% CI that includes possibility of no between-group difference or a substantial between-group difference
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).
d. Absolute risk differences calculated from odds ratios obtained using the Bucher method.

Table 2. IL12/23 (Ustekinumab) compared to IL17 (Brodalumab or Secukinumab) in patients with psoriasis

Bibliography: PICO 18: IL12/23i versus IL17i for PsA patients who failed OSM.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With IL12/23i	**With IL17i**		**Risk with IL12/23i**	**Risk difference with IL17i**
PASI-75											
1852 (2 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	427/613 (69.7%)	841/1239 (67.9%) **BROD**	**RR 0.98** (0.91 to 1.04)	697 per 1,000 (0.697)	**14 fewer per 1,000 (0.014)** (63 fewer to 28 more)
671 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	277/336 (82.4%)	311/335 (92.8%) **SEC**	**RR 1.12** (1.06 to 1.19) **Favors SEC**	824 per 1,000 (0.824)	**99 more per 1,000 (0.099)** (49 more to 157 more)
Infection											
671 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	85/336 (25.3%)	98/335 (29.3%) **SEC**	**RR 1.16** (0.90 to 1.49)	253 per 1,000 (0.253)	**40 more per 1,000 (0.040)** (25 fewer to 124 more)

CI: Confidence interval; **RR:** Risk ratio
a. Entire patient population was Psoriasis

Table 3. IL12/23i or IL17i compared to placebo for PICO 18: Adverse events

Bibliography: PICO 18: IL12/23i versus IL17i for PsA patients who failed OSM.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With IL12/23i or IL17i**		**Risk with placebo**	**Risk difference with IL12/23i or IL17i**
Serious infection – Ustekinumab vs. placebo											
925 (2 RCTs)	not serious	serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	2/309 (0.6%)	4/616 (0.6%)	**RR 0.84** (0.20 to 3.50) **No difference**	6 per 1,000 (0.006)	**1 fewer per 1,000** (5 fewer to 15 more)
Serious infection – IL17i vs. placebo											
1189 (3 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/406 (1.2%)	18/685 (2.6%)	**RR 1.79** (0.75 to 4.30)	12 per 1,000 (0.012)	**9 more per 1,000 (0.009)** (3 fewer to 52 more)

CI: Confidence interval; **RR:** Risk ratio
a. Comparison to placebo
b. Wide 95% CI that crosses line of no effect

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 19. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to MTX and TNFi combination therapy compared to switching to TNFi monotherapy?

Summary: This PICO was addressed by direct drug comparisons in 4 studies (2 RCTs, 1 post hoc analysis of 2 RCTs,[1,2,3] 1 observational[4]), but two of these studies had an indirect population (patients with psoriasis).[2,3] Three studies comparing MTX and TNFi (etanercept) combination therapy with TNFi (etanercept) monotherapy reported no statistically significant differences for three efficacy outcomes (ACR20, HAQ-DI, Physician Global). However, results for one efficacy outcome (PASI75) indicated a statistically significant difference in psoriasis patients at 24 weeks in one RCT,[2] but no statistically significant difference in PsA patients at 24 weeks in the post hoc analysis of two RCTs.[1] The psoriasis RCTs reported no statistically significant between-group difference for adverse events (serious infection, infection, hepatic events), but except for total infections the findings were imprecise.

Quality of evidence across all critical outcomes: Low

MTX + TNFi compared to TNFi monotherapy for PsA patients failed OSM (randomized)

Bibliography: PICO 19: MTX + TNFi combination vs. TNFi monotherapy for PsA patients failed OSM.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With TNFI mono-therapy	With MTX + TNFi		Risk with TNFI mono-therapy	Risk difference with MTX + TNFi
ACR20, 24 weeks											
431 (post hoc analysis of 2 RCTs)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	203/288 (70.5%)	100/143 (69.9%)	**RR 0.99** (0.87 to 1.13) **No difference**	705 per 1,000 (0.705)	**7 fewer per 1,000 (0.007)** (92 fewer to 92 more)
HAQ-DI [c], 24 weeks											

MTX + TNFi compared to TNFi monotherapy for PsA patients failed OSM (randomized)

Bibliography: PICO 19: MTX + TNFi combination vs. TNFi monotherapy for PsA patients failed OSM.

Quality assessment							Summary of findings				
436 (post hoc analysis of 2 RCTs)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	178/295 (60.3%)	92/141 (65.2%)	**RR 1.08** (0.93 to 1.26) **No difference**	603 per 1,000 (0.603)	**48 more per 1,000 (0.048)** (42 fewer to 157 more)
PASI 75, Psoriatic arthritis, 24 weeks											
406 (post hoc analysis of 2 RCTs)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	166/278 (59.7%)	75/128 (58.6%)	**RR 0.98** (0.80 to 1.15) **No difference**	597 per 1,000 (0.597)	**12 fewer per 1,000 (0.012)** (119 fewer to 90 more)
PASI 75, Psoriasis, 24 weeks											
537 (2 RCTs)	serious [d]	not serious	serious [e]	not serious	none	⨁⨁◯◯ LOW	167/267 (62.5%)	213/270 (78.9%)	**RR 1.26** (1.11 to 1.44) **Favors MTX + TNFi**	625 per 1,000 (0.625)	**163 more per 1,000 (0.163)** (69 more to 275 more)
Serious Infection, Psoriasis											
59 (1 RCT)	not serious	not serious	serious [e]	serious [f]	none	⨁⨁◯◯ LOW	1/28 (3.6%)	0/31 (0.0%)	**RR 0.30** (0.01 to 7.13)	36 per 1,000 (0.036)	**25 fewer per 1,000 (0.025)** (35 fewer to 219 more)

MTX + TNFi compared to TNFi monotherapy for PsA patients failed OSM (randomized)

Bibliography: PICO 19: MTX + TNFi combination vs. TNFi monotherapy for PsA patients failed OSM.

Quality assessment							Summary of findings				
Infections, 24 weeks, Psoriasis											
478 (1 RCT)	not serious	not serious	serious [e]	not serious	none	⨁⨁⨁◯ MODERATE	62/239 (25.9%)	83/239 (34.7%)	**RR 1.34** (1.02 to 1.76) **Favors TNFi mono**	259 per 1,000	**88 more per 1,000 (0.088)** (5 more to 197 more)
Hepatic adverse event (increased transminases), 24 weeks, Psoriasis											
478 (1 RCT)	not serious	not serious	serious [e]	serious [f]	none	⨁⨁◯◯ LOW	4/239 (1.7%)	7/239 (2.9%)	**RD 0.01 (-0.01 to 0.04)** **RR 1.75** (0.52 to 5.90)	17 per 1,000 (0.017)	**10 more per 1,000 (0.010)** (10 fewer to 40 more)

CI: Confidence interval; **RR:** Risk ratio

a. Both RCTs contributing data to this post hoc analysis did not describe randomization methods or allocation concealment methods, and 1 trial did not report blinding of outcome assessors.

b. Indirect comparison of treatment arms from 2 placebo-controlled RCTs.

c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

d. Open label study

e. Indirect population (Psoriasis patients)

f. Low number of events

MTX + TNFi compared to TNFi monotherapy for PsA patients failed OSM (observational)

Bibliography: PICO 19: MTX + TNFi combination vs. TNFi monotherapy for PsA patients failed OSM.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With TNFi monotherapy	**With MTX + TNFi**		**Risk with TNFi monotherapy**	**Risk difference with MTX + TNFi**
HAQ-DI, 24 weeks											
284 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	52/98 (53.1%)	98/186 (52.7%)	**RR 0.99** (0.79 to 1.25) **No difference**	531 per 1,000 (0.531)	**5 fewer per 1,000 (0.005)** (111 fewer to 133 more)
Physician global, 24 weeks											
284 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	98 patients MD -24.7 (21.4)	186 patients MD -22.2 (22.3)	-		MD **2.5 higher** (2.81 lower to 7.81 higher)

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Selection bias and confounding by indication

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 20. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to MTX and IL12/23i combination therapy compared to switching to IL12/23i monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 21. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to MTX and IL17i combination therapy compared to switching to IL17i monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 22. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to another OSM monotherapy compared to adding another OSM?

Summary: This PICO question was addressed by indirect comparisons in three RCTs.[1-3] All trials had placebo groups that continued to receive whatever prior OSMs they had been receiving, rather than being switched to a new OSM. One RCT comparing MTX and cyclosporine combination therapy with MTX monotherapy plus placebo reported no statistically significant difference in nausea, but there was imprecision in the effect size estimate.[1] Two RCTs comparing apremilast with placebo included a subgroup analysis of patients receiving other OSMs concomitantly with apremilast or placebo. Together these subgroup analyses found a statistically significant difference favoring apremilast over placebo for one efficacy outcome (ACR20) at 16 weeks.[2,3]

Quality of evidence across all critical outcomes: Low

MTX compared to MTX + Cyclosporine (CSA) for PsA patients who failed OSM

Bibliography: PICO 22: OSM monotherapy versus combination OSM for PsA patients failed OSM.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With MTX + CSA	**With MTX + placebo**		**Risk with MTX + CSA**	**Risk difference with MTX + placebo**
Nausea, 52 weeks											
72 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	15/38 (39.5%)	6/34 (17.6%)	**RR 0.45** (0.20 to 1.02)	395 per 1,000 (0.395)	**217 fewer per 1,000 (0.217)** (316 fewer to 8 more)

CI: Confidence interval; **RD:** Risk difference

a. All patients had failed to have a partial response to MTX prior to enrollment, so patients in the MTX + placebo group were not "switched" to MTX.

b. Small study that does not meet optimal information size, wide CI

Apremilast plus other OSMs compared to placebo plus other OSMs for PsA patients who failed OSM

Bibliography: PICO 22: OSM monotherapy versus combination OSM for PsA patients failed OSM.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo + OSM	**With apremilast + other OSM**		**Risk with placebo**	**Risk difference with apremilast**
ACR20, 16 weeks											
428 (2 RCTs)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	45/214 (21.0%)	83/214 (38.8%)	**RR 1.84** (1.35 to 2.51) **Favors apremilast + other OSM**	210 per 1,000 (0.210)	**177 more per 1,000 (0.177)** (74 more to 318 more)

CI: Confidence interval; **RR:** Risk ratio

a. Unclear randomization, allocation concealment, and blinding of patients/providers/assessors in 1 RCT[2]. Both studies not consistent with calculating outcomes for ITT populations.

b. Patients in the placebo group were not actually switched to a different OSM, they continued treatment with the same OSM(s).

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 23. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to a different OSM compared to switching to a TNFi?

Summary. Only one study directly compared a TNFi to an OSM in patients with PsA[1]. This study, which compared cyclosporine and adalimumab, was an unblinded observational study with only partial randomization of enrollees (see footnote in Table 2 for further details). We therefore included two RCTs comparing TNFi to an OSM in patients with psoriasis[2,3] as well as a number of RCTs comparing TNFi or OSM to placebo in patients with PsA. Most of the data presented for this PICO is therefore indirect in nature. Nine RCTs (12 publications) comparing TNFi to placebo were included for this PICO.[4-15] Five RCTs compared OSM to placebo: one compared leflunomide to placebo[16,17], and four compared apremilast to placebo[18-23].

A network meta-analysis was performed to indirectly compare OSMs vs TNFis using the placebo-controlled RCTs noted above (Table 1). Due to considerable heterogeneity in findings among different TNFIs for ACR20, HAQ-DI and PASI-75, these drugs were separated in the network meta-analysis. Of individual TNFIs, golimumab and infliximab were associated with significantly greater numbers of patients who achieved ACR20 and PASI75 compared to the OSM group. Only adalimumab and infliximab were associated with significantly greater numbers of patients who achieved minimum change in HAQ-DI. The remaining individual TNFIs did not show superiority over the OSM group for any outcomes, although imprecision in the findings means that a between-group difference could not be ruled out (data not shown). An updated literature search in March 2018 identified one additional RCT showing superiority of golimumab over placebo[24]. This trial had not been previously reviewed by the panel, but it was moderate quality (due to indirectness) and the results did not change the overall findings or the overall quality of evidence.

The single observational study directly comparing an OSM to a TNFi found cyclosporine to be significantly better than adalimumab for improvement in PASI75. No other outcomes showed significant between-group differences, although there was imprecision in the effect estimates. One RCT of psoriasis patients found a significant benefit of etanercept over 5 mg tofacitinib for improving PASI75 (Table 2).

Adverse events could not be compared using adjusted indirect comparison because the trials of different drug classes did not report similar adverse events. Both apremilast and leflunomide showed a slightly greater risk of causing liver toxicity compared to placebo when combined in a meta-analysis. Apremilast also caused increased GI discomfort compared to placebo (Table 3).

No trial stratified outcomes by history of exposure or failure of OSMs, but a few TNFi vs placebo and apremilast vs placebo RCTs reported outcomes by history of exposure to biologic agents. In the limited data available, TNFi blockers and apremilast seem to work as well in biologic-experienced compared to biologic-naïve patients.

Quality of evidence across all critical outcomes: Moderate

Table 1. Different OSM compared to TNFi for patients with active PsA despite OSM

Bibliography: PICO 23: Different OSM compared to TNFi for patients with active PsA despite OSM

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							OSM	TNFi		Risk with OSM	Risk difference with TNFi
ACR20, 12-24 weeks, network meta-analysis											
1539 (6 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	OSM	GOL	**RR 2.60** (1.29 to 5.26) **Favors GOL**	380 per 1,000 (0.380)	**321 more per 1000 (0.321)** (139 more to 456 more)[b]
1638 (8 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	OSM	IFX	**RR 3.40** (2.10 to 5.51) **Favors IFX**	380 per 1,000 (0.380)	**464 more per 1000 (0.464)** (185 more to 578 more)[b]
HAQ-DI[c], 12-24 weeks, network meta-analysis											
1580 (6 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	OSM	ADA	**RR 1.43** (1.06 to 1.94) **Favors ADA**	394 per 1,000 (0.394)	**169 more per 1000 (0.169)** (24 more to 370 more)

Table 1. Different OSM compared to TNFi for patients with active PsA despite OSM

Bibliography: PICO 23: Different OSM compared to TNFi for patients with active PsA despite OSM

Quality assessment							Summary of findings				
1367 (5 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	OSM	IFX	**RR 1.79** (1.21 to 2.64) **Favors IFX**	394 per 1,000 (0.394)	**224 more per 1000 (0.224)** (58 more to 367 more) [b]
PASI 75, 12-24 weeks, network meta-analysis											
1026 (5 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	OSM	GOL	**RR 4.74** (1.07 to 21.01) **Favors GOL**	164 per 1,000 (0.164)	**405 more per 1000 (0.405)** (54 more to 698 more) [b]
1062 (6 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	OSM	IFX	**RR 8.23** (2.14 to 31.65) **Favors IFX**	164 per 1,000 (0.164)	**631 more per 1000 (0.631)** (320 more to 777 more) [b]

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Absolute risk differences calculated from odds ratios obtained using the Bucher method.
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

Table 2. OSM compared to TNFi for patients with active PsA despite OSM

Bibliography: PICO 23: In patients with active PsA despite OSM, benefit/harm of switching to different OSM compared to TNFi.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With TNFi	With OSM		Risk with TNFi	Risk difference with OSM
ACR20 - Cyclosporine vs TNFi (Adalimumab)											
115 (1 study)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	45/58 (77.6%)	36/57 (63.2%)	**RR 0.81** (0.64 to 1.04)	776 per 1,000 (0.776)	**147 fewer per 1,000 (0.147)** (279 fewer to 31 more)
PASI 75 – Apremilast versus TNFi (Etanercept)											
166 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	40/83 (48.2%)	33/83 (39.8%)	**RR 0.82** (0.58 to 1.17)	482 per 1,000	**87 fewer per 1,000** (202 fewer to 82 more)
PASI-75 - Tofacitinib vs TNFi (Etanercept)											
664 (1 RCT)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	197/335 (58.8%)	130/329 (39.5%)	**RR 0.67** (0.57 to 0.79) **Favors ETN**	588 per 1,000 (0.588)	**194 fewer per 1,000 (0.194)** (253 fewer to 123 fewer)
PASI-75 - Cyclosporine vs TNFi (Adalimumab)											

Table 2. OSM compared to TNFi for patients with active PsA despite OSM

Bibliography: PICO 23: In patients with active PsA despite OSM, benefit/harm of switching to different OSM compared to TNFi.

Quality assessment							Summary of findings				
84 (1 study)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	9/43 (20.9%)	18/41 (43.9%)	**RR 2.10** (1.07 to 4.12)	209 per 1,000 (0.209)	**230 more per 1,000 (0.230)** (15 more to 653 more)
HAQ-DI[d] - Cyclosporine vs TNFi (Adalimumab)											
115 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	43/58 (74.1%)	33/57 (57.9%)	**RR 0.78** (0.60 to 1.02)	741 per 1,000 (0.741)	**163 fewer per 1,000 (0.163)** (297 fewer to 15 more)
Serious adverse events - Tofacitinib vs TNFi (Etanercept)											
664 (1 RCT)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	7/335 (2.1%)	7/329 (2.1%)	**RR 1.02** (0.36 to 2.87)	21 per 1,000 (0.021)	**0 more per 1,000** (13 fewer to 39 more)
Liver toxicity[e] - Cyclosporine vs TNFi (Adalimumab)											
115 (1 study)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	5/58 (8.6%)	3/57 (5.3%)	**RR 0.61** (0.15 to 2.44)	86 per 1,000 (0.086)	**34 fewer per 1,000 (0.034)** (73 fewer to 124 more)

Table 2. OSM compared to TNFi for patients with active PsA despite OSM

Bibliography: PICO 23: In patients with active PsA despite OSM, benefit/harm of switching to different OSM compared to TNFi.

Quality assessment							Summary of findings				
Serious infection - OSM vs TNFi											
945 (3 RCTs)	Not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	4/476 (0.8%)	3/469 (0.6%)	**RR 0.81** (0.20 to 3.38)	8 per 1,000 (0.008)	**2 fewer per 1,000 (0.002)** (6 fewer to 19 more)

CI: Confidence interval; **RR:** Risk ratio

a. The Karanikolas et al 2011 cyclosporine vs adalimumab study[1] is an unblinded clinical trial in which most but not all patients were randomized to treatment groups. Specifically, 76 patients were randomly assigned to cyclosporine, adalimumab, or combination therapy. The remaining 94 patients were not randomly assigned: 32 patients could not receive adalimumab due to insurance restrictions, so they were assigned to cyclosporine. The remaining 62 patients were randomly assigned to adalimumab (32 patients) and combination therapy (30 patients).

b. The Bachelez 2015 tofacitinib vs etanercept RCT[2] and the Reich apremilast vs. etanercept RCT[3] focused on patients with plaque psoriasis, not psoriatic arthritis.

c. Wide CI that crosses line of no effect

d. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

e. Alanine aminotransferase or aspartate aminotransferase value ≥ 3 times upper limit of normal.

Table 3. OSM or TNFi compared to placebo for PICO 23: Adverse events

Bibliography: PICO 23: In patients with active PsA despite OSM, benefit/harm of switching to different OSM compared to TNFi.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With TNFi or OSM**		**Risk with placebo**	**Risk difference with TNFi or OSM**

Table 3. OSM or TNFi compared to placebo for PICO 23: Adverse events

Bibliography: PICO 23: In patients with active PsA despite OSM, benefit / harm of switching to different OSM compared to TNFi.

Quality assessment							Summary of findings				
Serious infections – TNFi vs. placebo											
1151 (5 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	8/564 (1.4%)	4/587 (0.7%)	**RR 0.54** (0.17 to 1.77) **No difference**	14 per 1,000 (0.014)	**6 fewer per 1,000 (0.006)** (12 fewer to 11 more)
Liver toxicity[d] – OSM vs. placebo											
1309 (5 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	6/652 (0.9%)	19/657 (2.9%)	**RR 2.58** (1.13 to 5.85) **Favors placebo**	9 per 1,000 (0.009)	**15 more per 1,000 (0.015)** (1 more to 45 more)
GI intolerance (diarrhea and nausea) – OSM vs. placebo											
1308 (5 RCTs)	not serious	serious [c]	serious [a]	not serious	none	⨁⨁◯◯ LOW	76/646 (11.8%)	220/662 (33.2%)	**RR 2.71** (1.62 to 4.52) **Favors placebo**	118 per 1,000 (0.118)	**202 more per 1,000 (0.169)** (73 more to 415 more)
GI intolerance (diarrhea and nausea) - Apremilast vs placebo											

Table 3. OSM or TNFi compared to placebo for PICO 23: Adverse events

Bibliography: PICO 23: In patients with active PsA despite OSM, benefit / harm of switching to different OSM compared to TNFi.

Quality assessment							Summary of findings				
1120 (4 RCTs)	not serious	serious	serious [a]	not serious	none	⊕⊕⊕◯ MODERATE	56/554 (10.1%)	188/566 (33.2%)	**RR 3.15** (1.79 to 5.54) **Favors placebo**	101 per 1,000 (0.101)	**217 more per 1,000 (0.217)** (80 more to 459 more)

CI: Confidence interval; **RR:** Risk ratio

a. Comparison to placebo

b. Wide confidence intervals due to low event rates

c. The study of leflunomide had a RR of 1.53 (0.95-2.48) whereas the studies of apremilast showed a higher risk, with an overall RR of 3.15 (1.79 to 5.54)

d. Studies had slightly different cutoffs for abnormality: ALT ≥1.5 times the upper normal limit (1 study), ALT > 150 u/l (2 studies), ALT >upper normal limit (1 study)

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 24. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to a different OSM compared to switching to an IL12/23i?

Summary. No studies directly compared IL12/23i with an OSM. Eight placebo-controlled RCTs provided indirect evidence for this question: three RCTs of ustekinumab[1-3], and 5 RCTs of OSMs (apremilast, 4 RCTs[4-9], and leflunomide, 1 RCT[10,11]). A majority of patients in most studies had a history of OSM use. None of the studies stratified outcomes by history of OSM use, which also contributes to indirectness of the data relative to the PICO question. For all studies we used data for drug dosages that were closest to standard clinical practice.

A network meta-analysis was performed to indirectly compare OSMs vs IL12/23i using the placebo-controlled RCTs noted above. The meta-analysis found a significant difference favoring IL12/23i for HAQ-DI, but no significant between-class differences in ACR20 or PASI 75 outcomes (these findings were inconclusive due to imprecision in the wide CIs that cross the line of no effect) (Table 1).

Adverse events could not be compared using adjusted indirect comparison because the trials of different drug classes did not report similar adverse events. Ustekinumab trials reported rates of infection while OSM trials reported liver toxicity and gastrointestinal (GI) discomfort. Comparing adverse events in drug versus placebo groups, ustekinumab did not demonstrate any increase in severe infection rates compared to placebo. Both apremilast and leflunomide showed a slightly greater risk of causing liver toxicity compared to placebo when combined in a meta-analysis. Apremilast also caused increased GI discomfort compared to placebo (Table 2).

Quality of evidence across all critical outcomes: Low

Table 1. Different OSM compared to IL12/23i for patients with active PsA despite OSM
Bibliography: PICO 24: Different OSM compared to IL12/23i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							OSM	IL12/23i		Risk with OSM	Risk difference with IL12/23i
ACR20, 12-24 weeks, network meta-analysis											

Table 1. Different OSM compared to IL12/23i for patients with active PsA despite OSM

Bibliography: PICO 24: Different OSM compared to IL12/23i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
2353 (8 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	**OSM**	**IL12/23i**	**RR 1.06** (0.67 to 1.70)	380 per 1,000 (0.380)	**23 more per 1000 (0.023)** (125 fewer to 266 more)
HAQ-DI[c], 12-24 weeks, network meta-analysis											
2233 (7 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	**OSM**	**IL12/23i**	**RR 1.37** (1.00 to 1.88) **Favors IL12/23i**	394 per 1,000 (0.394)	**146 more per 1,000 (0.146)** (0 more to 347 more)
PASI 75, 12-24 weeks, network meta-analysis											
1637 (7 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	**OSM**	**IL12/23i**	**RR 2.01** (0.70 to 5.76)	164 per 1,000 (0.164)	**166 more per 1000 (0.166)** (49 fewer to 781 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, in most studies only 50-75% of patients had prior OSM exposure.
b. Wide CI that overlaps line of no difference
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

Table 2. OSM (apremilast or leflunomide) or IL12/23i compared to placebo for PICO 24: Adverse events

Bibliography: PICO 24: In patients with active PsA despite OSM, benefit/harm of switching to different OSM compared to IL-12/23i.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With drug**		**Risk with placebo**	**Risk difference with OSM**
Serious infections – Ustekinumab vs. placebo											
925 (2 RCTs)	not serious	serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	2/309 (0.6%)	4/616 (0.6%)	**RR 0.84** (0.20 to 3.50) **No difference**	6 per 1,000 (0.006)	**1 fewer per 1,000** (5 fewer to 15 more)
Liver toxicity[d] – OSM vs. placebo											
1309 (5 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	6/652 (0.9%)	19/657 (2.9%)	**RR 2.58** (1.13 to 5.85) **Favors placebo**	9 per 1,000 (0.009)	**15 more per 1,000 (0.015)** (1 more to 45 more)
GI intolerance (diarrhea and nausea) – OSM vs. placebo											

Table 2. OSM (apremilast or leflunomide) or IL12/23i compared to placebo for PICO 24: Adverse events

Bibliography: PICO 24: In patients with active PsA despite OSM, benefit/harm of switching to different OSM compared to IL-12/23i.

Quality assessment							Summary of findings				
1308 (5 RCTs)	not serious	serious [c]	serious [a]	not serious	none	⨁⨁◯◯ LOW	76/646 (11.8%)	220/662 (33.2%)	**RR 2.71** (1.62 to 4.52) **Favors placebo**	118 per 1,000 (0.118)	**202 more per 1,000 (0.169)** (73 more to 415 more)
GI intolerance (diarrhea and nausea) - Apremilast vs placebo											
1120 (4 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	56/554 (10.1%)	188/566 (33.2%)	**RR 3.15** (1.79 to 5.54) **Favors placebo**	101 per 1,000 (0.101)	**217 more per 1,000 (0.217)** (80 more to 459 more)

CI: Confidence interval; **RR:** Risk ratio

a. Comparison to placebo

b. Wide confidence intervals due to low event rate in both groups

c. The study of leflunomide had a RR of 1.53 (0.95-2.48) whereas the studies on apremilast showed a higher risk, with an overall of 3.15 (1.79-5.54)

d. Studies had slightly different cutoffs for abnormality: ALT ≥1.5 times the upper normal limit (1 study), ALT > 150 u/l (2 studies), ALT >upper normal limit (1 study)

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 25. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to a different OSM monotherapy compared to switching to an IL17i?

Summary: This PICO was addressed indirectly by 16 double-blind RCTs. Eight studies involving PsA patients or psoriasis patients compared IL17i to placebo.[1-8] One study compared IL17i to TNFi.[8] The outcomes measured when available were ACR20, PASI-75, HAQ-DI, and adverse events. All drugs showed statistically significant improvements in ACR20, PASI-75, and HAQ-DI over placebo (data not shown), with no significant between-group difference in adverse events. Eight studies involving PsA patients compared OSMs (apremilast and leflunomide) to placebo.[9-16] Both OSMs showed statistically significant improvements in ACR20, PASI-75, and HAQ-DI over placebo (data not shown). Liver toxicity was significantly greater in patients receiving OSM compared to placebo. GI intolerance did not differ significantly between leflunomide and placebo patients, but a significantly increased risk appeared among patients receiving apremilast compared to patients receiving placebo (Table 2).

A network meta-analysis was performed to indirectly compare OSMs vs IL17is using the placebo-controlled RCTs noted above (Table 1). Although the meta-analysis found no significant difference between drug classes for ACR20 and HAQ DI, the findings are inconclusive due to imprecision in the effect estimates. For PASI75, although heterogeneity was detected among studies of secukinumab, the findings showed a significant benefit of IL17is over OSMs for improvement in this outcome. Although there was no substantial heterogeneity among IL17i studies for ACR20, the effect sizes were larger in trials of secukinumab compared to trials of ixekizumab and brodalumab. Therefore, we used the Bucher adjusted indirect comparison method to compare OSMs to secukinumab alone. This analysis found a significant benefit of secukinumab over OSMs for improvement in ACR20.

Quality of evidence across all critical outcomes: Low

Table 1. Different OSM compared to IL17i for patients with active PsA despite OSM
Bibliography: PICO 25: Different OSM compared to IL17i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							OSM	IL17i		Risk with OSM	Risk difference with IL17i
ACR20, 12-24 weeks, network meta-analysis											

Table 1. Different OSM compared to IL17i for patients with active PsA despite OSM

Bibliography: PICO 25: Different OSM compared to IL17i for patients with active PsA despite OSM

Quality assessment							Summary of findings				
2162 (11 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	**OSM**	**IL17i**	**RR 1.19** (0.71 to 2.00)	386 per 1,000 (0.386)	**73 more per 1000 (0.073)** (112 fewer to 386 more)
ACR20, 12-24 weeks, Bucher adjusted indirect comparison – OSM versus Secukinumab											
1828 (8 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	**OSM**	**SEC**	**RR 1.49** (1.07 to 2.09) **Favors SEC**	386 per 1,000 (0.386)	**189 more per 1000 (0.189)**(27 more to 421 more)
HAQ-DI[c], 12-24 weeks, network meta-analysis											
2014 (8 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	**OSM**	**IL17i**	**RR 1.11** (0.82 to 1.52)	394 per 1,000 (0.394)	**43 more per 1000 (0.043)** (71 fewer to 205 more)
PASI 75, 12-24 weeks, network meta-analysis											
1576 (8 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	**OSM**	**IL17i**	**RR 2.41** (1.02 to 5.74) **Favors IL17i**	164 per 1,000 (0.164)	**231 more per 1000 (0.231)** (3 more to 777 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide CI that overlaps line of no difference
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

Table 2. OSM (apremilast or leflunomide) or IL17i compared to placebo for PICO 25: Adverse events

Bibliography: PICO 25: In patients with active PsA despite OSM, benefit/harm of switching to different OSM compared to IL-17i.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With IL17i or OSM**		**Risk with placebo**	**Risk difference with IL17i or OSM**
Serious infection – IL17i vs. placebo											
1189 (3 RCTs)	not serious	not serious	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	5/406 (1.2%)	18/685 (2.6%)	**RR 1.79** (0.75 to 4.30)	12 per 1,000 (0.012)	**9 more per 1,000 (0.009)** (3 fewer to 52 more)
Liver toxicity[d] – OSM vs. placebo											
1309 (5 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	6/652 (0.9%)	19/657 (2.9%)	**RR 2.58** (1.13 to 5.85) **Favors placebo**	9 per 1,000 (0.009)	**15 more per 1,000 (0.015)** (1 more to 45 more)

Table 2. OSM (apremilast or leflunomide) or IL17i compared to placebo for PICO 25: Adverse events

Bibliography: PICO 25: In patients with active PsA despite OSM, benefit/harm of switching to different OSM compared to IL-17i.

Quality assessment							Summary of findings				
GI intolerance (diarrhea and nausea) – OSM vs. placebo											
1308 (5 RCTs)	not serious	serious [c]	serious [a]	not serious	none	⨁⨁◯◯ LOW	76/646 (11.8%)	220/662 (33.2%)	**RR 2.71** (1.62 to 4.52) **Favors placebo**	118 per 1,000 (0.118)	**202 more per 1,000 (0.169)** (73 more to 415 more)
GI intolerance (diarrhea and nausea) - Apremilast vs placebo											
1120 (4 RCTs)	not serious	serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	56/554 (10.1%)	188/566 (33.2%)	**RR 3.15** (1.79 to 5.54) **Favors placebo**	101 per 1,000 (0.101)	**217 more per 1,000 (0.217)** (80 more to 459 more)

CI: Confidence interval; **RR:** Risk ratio

a. Comparison to placebo

b. Wide CI that overlaps the line of no effect

c. The study of leflunomide had a RR of 1.53 (0.95-2.48) whereas the studies on apremilast showed a higher risk, with an overall of 3.15 (1.79-5.54)

d. Studies had slightly different cutoffs for abnormality: ALT ≥1.5 times the upper normal limit (1 study), ALT > 150 u/l (2 studies), ALT >upper normal limit (1 study)

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 26. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to a second TNFi + MTX compared to adding MTX to the same TNFi monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 26 (alternate). In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to a second TNFi monotherapy compared to adding MTX to the same TNFi monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 27. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to a second TNFi compared to switching to IL12/23i?

Summary: This PICO question was addressed indirectly by three double-blind RCTs (4 publications). In addition to lack of direct drug comparisons, only 19% to 50% of patients in each study had prior TNFi exposure. One study (2 publications) involving PsA patients compared TNFi (certolizumab pegol [CZP]) to placebo.[1,2] Two studies involving PsA patients compared IL12/23i to placebo.[3,4] The outcomes measured when available were ACR20, PASI-75, HAQ-DI, serious infections and infections. All drugs showed statistically significant improvements in ACR20, PASI-75, and HAQ-DI over placebo; for serious infections there were no significant between-group differences, but with very high imprecision due to the low number of events (data not shown).

The adjusted indirect comparison method was used to calculate RRs for CZP vs. ustekinumab. For ACR20 we also performed this calculation using data only from patients with prior TNFi exposure (a few studies reported separate data for these patients). Ustekinumab showed a significant benefit over CZP for HAQ-DI and PASI-75, but not for ACR20 or rate of infection (see table below).

Quality of evidence across all critical outcomes: Low

TNFi compared to IL12/23i for patients with active PsA despite prior TNFi

Bibliography: PICO 27: TNFi compared to IL12/23i for patients with active PsA despite prior TNFi

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With IL12/23i	**With TNFi**		**Risk with IL12/23i**	**Risk difference with TNFi**
ACR20, 12-24 weeks, Bucher adjusted indirect comparison											
732 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	CZP	**RR 1.00** (0.62 to 1.60)	433 per 1,000 (0.433)	**0 more per 1000** (165 fewer to 260 more)
ACR20, 12-24 weeks, Bucher adjusted indirect comparison, TNFi-exposed patients											

TNFi compared to IL12/23i for patients with active PsA despite prior TNFi

Bibliography: PICO 27: TNFi compared to IL12/23i for patients with active PsA despite prior TNFi

Quality assessment							Summary of findings				
260 (2 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	CZP	IL12/23i	**RR 0.32** (0.01 to 2.52)	296 per 1,000 (0.296)	**201 fewer per 1000** (293 fewer to 450 more)
HAQ-DI[c], 12-24 weeks, Bucher adjusted indirect comparison											
725 (3 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL12/23i	CZP	**RR 0.63** (0.41 to 0.97) **Favors IL12/23i**	389 per 1,000 (0.389)	**144 fewer per 1000 (0.144)** (230 fewer to 12 fewer)
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
535 (3 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL12/23i	CZP	**RR 0.32** (0.13 to 0.83) **Favors IL12/23i**	531 per 1,000 (0.531)	**361 fewer per 1000 (0.361)** (462 fewer to 90 fewer)
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
(3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	CZP	**RR 1.01** (0.61 to 1.67)	271 per 1,000 (0.271)	**3 more per 1000 (0.003)** (106 fewer to 182 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 28. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to a second TNFi compared to switching to IL17i?

Summary: This PICO was addressed indirectly by six double-blind RCTs (in 7 publications). In addition to lack of direct drug comparisons, only 28% to 50% of patients in each study had prior TNFi exposure. One study (in 2 publications) involving PsA patients compared TNFi (CZP) to placebo.[1,2] Two studies involving PsA patients compared Brodalumab to placebo.[3,4] Three studies compared Secukinumab to Placebo.[5-7] All drugs showed statistically significant improvements in ACR20, PASI-75, and HAQ-DI over placebo (data not shown).

The adjusted indirect comparison method was used to calculate RRs for CZP vs. IL17i (see table below). For ACR20 we also performed this calculation using data only from patients with prior TNFi exposure (a few studies reported separate data for these patients). The analyses found no significant differences in ACR20, HAQ-DI, PASI-75, or total infections, but almost all effect sizes were imprecise due to wide confidence intervals.

Quality of evidence across all critical outcomes: Low

TNFi compared to IL17i for patients with active PsA despite prior TNFi

Bibliography: PICO 28: TNFi compared to IL17i for patients with active PsA despite prior TNFi

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**			**Relative effect (95% CI)**	**Anticipated absolute effects**	
							IL17i	**TNFi**		**Risk with IL17i**	**Risk difference with TNFi**
ACR20, 12-24 weeks, Bucher adjusted indirect comparison											
1022 (5 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	**IL17i**	CZP	**RR 0.85** (0.56 to 1.28)	479 per 1,000 (0.479)	**72 fewer per 1000 (0.072)** (211 fewer to 134 more)

TNFi compared to IL17i for patients with active PsA despite prior TNFi

Bibliography: PICO 28: TNFi compared to IL17i for patients with active PsA despite prior TNFi

Quality assessment							Summary of findings				
ACR20, 12-24 weeks, Bucher adjusted indirect comparison, TNFi-exposed patients											
270 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	**CZP**	IL17i	**RR 0.33** (0.04 to 2.55)	296 per 1,000 (0.296)	**198 fewer per 1000** (284 fewer to 459 more)
HAQ-DI[c], 12-24 weeks, Bucher adjusted indirect comparison											
910 (4 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	**IL17i**	CZP	**RR 1.05** (0.78 to 1.40)	545 per 1,000 (0.545)	**27 more per 1000 (0.027)** (120 fewer to 218 more)
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
494 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	**IL17i**	CZP	**RR 0.70** (0.24 to 2.05)	566 per 1,000 (0.566)	**140 fewer per 1000 (0.140)** (421 fewer to 197 more)[d]
Infection, 12-24 weeks, Bucher adjusted indirect comparison											

TNFi compared to IL17i for patients with active PsA despite prior TNFi

Bibliography: PICO 28: TNFi compared to IL17i for patients with active PsA despite prior TNFi

Quality assessment							Summary of findings				
876 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	**IL17i**	CZP	**RR 0.94** (0.59 to 1.50)	321 per 1,000 (0.321)	**19 fewer per 1000 (0.019)** (132 fewer to 161 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).
d. Absolute risk difference and confidence interval calculated based on the odds ratio.

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 29. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to an IL12/23i compared to switching to IL17i?

Summary: This PICO was addressed indirectly by 8 double-blind RCTs involving PsA patients or psoriasis patients compared either IL12/23i or IL17i to placebo.[1-8] In addition to lack of direct drug comparisons, only one study[8] included 100% of patients with prior TNFi exposure; the remaining studies included only 28% to 50% of patients with prior TNFi exposure. All drugs showed statistically significant improvements in ACR20, PASI-75, and HAQ-DI over placebo, while adverse event rates did not differ significantly between the two groups (data not shown).

The adjusted indirect comparison method was used to calculate RRs for IL12/23i vs. IL17i (see table below). For ACR20 we also performed this calculation using data only from patients with prior TNFi exposure (a few studies reported separate data for these patients). No significant between-class difference was observed for the outcomes ACR20, HAQ-DI, PASI75, and total infections, but all of these findings were inconclusive due to imprecision in the effect estimates.

Quality of evidence across all critical outcomes: Low

IL12/23i compared to IL17i for patients with active PsA despite prior TNFi

Bibliography: PICO 29: IL12/23i compared to IL17i for patients with active PsA despite prior TNFi

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**			**Relative effect (95% CI)**	**Anticipated absolute effects**	
							IL12/23i	**IL17i**		**Risk with IL12/23i**	**Risk difference with IL17i**
ACR20, 12-24 weeks, Bucher adjusted indirect comparison											
662 (5 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	**IL12/23i**	**IL17i**	**RR 1.19** (0.79 to 1.80)	381 per 1,000 (0.381)	**72 more per 1000 (0.072)** (80 fewer to 305 more)
ACR20, 12-24 weeks, Bucher adjusted indirect comparison, TNFi-exposed patients											

IL12/23i compared to IL17i for patients with active PsA despite prior TNFi

Bibliography: PICO 29: IL12/23i compared to IL17i for patients with active PsA despite prior TNFi

Quality assessment							Summary of findings				
611 (4 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⊕⊕◯◯ LOW	**IL12/23i**	**IL17i**	**RR 0.97** (0.47 to 2.00)	356 per 1,000 (0.356)	**11 fewer per 1000 (0.011)**(189 fewer to 356 more)
HAQ-DI[c], 12-24 weeks, Bucher adjusted indirect comparison											
1089 (5 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⊕⊕◯◯ LOW	**IL12/23i**	**IL17i**	**RR 0.68** (0.44 to 1.07)	389 per 1,000 (0.389)	**124 fewer per 1000 (0.124)** (218 fewer to 27 more)
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
639 (5 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⊕⊕◯◯ LOW	**IL12/23i**	**IL17i**	**RR 0.52** (0.22 to 1.22)	493 per 1,000 (0.493)	**237 fewer per 1000 (0.237)** (385 fewer to 108 more)
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
913 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⊕⊕◯◯ LOW	**IL12/23i**	**IL17i**	**RR 1.07** (0.62 to 1.85)	271 per 1,000 (0.271)	**19 more per 1000 (0.019)** (103 fewer to 230 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, in some studies the majority of patients did not have prior TNFi exposure and data was not reported separately for those with TNFi exposure.
b. Wide 95% CI
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009;373(9664):633-640.
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6. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73(6):990-999.
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8. Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester G, Adams DH, Kerr L, Lee C, Shuler CL, Genovese M on behalf of the SPIRIT-P2 Study Group. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet 2017; 389:2317-2327.

PICO 30. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to a second TNFi and MTX combination therapy compared to a second TNFi monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 31. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to MTX and IL12/23i combination therapy compared to switching to IL12/23i monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 32. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to MTX and IL17i combination therapy compared to switching to IL17i monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 33. In adult patients with active PsA despite treatment with a TNFi and MTX combination therapy,, what are the benefits and harms of switching to a second TNFi and MTX combination therapy compared to switching to a second TNFi monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 34. In adult patients with active PsA despite treatment with a TNFi and MTX combination therapy,, what are the benefits and harms of switching to MTX and IL12/23i combination therapy compared to switching to IL12/23i monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 35. In adult patients with active PsA despite treatment with a TNFi and MTX combination therapy, what are the benefits and harms of switching to MTX and IL17i combination therapy compared to switching to IL17i monotherapy?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 36. In adult patients with active PsA despite treatment with an IL23/23i, what are the benefits and harms of adding MTX to the IL12/23i compared to switching to TNFi?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 37. In adult patients with active PsA despite treatment with an IL23/23i, what are the benefits and harms of adding MTX to the IL12/23i compared to switching to IL17i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 38. In adult patients with active PsA despite treatment with an IL23/23i, what are the benefits and harms of switching to a TNFi compared to switching to IL17i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 39. In adult patients with active PsA despite treatment with an IL17i, what are the benefits and harms of switching to a TNFi compared to switching to IL12/23i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 40. In adult patients with active PsA despite treatment with an IL17i, what are the benefits and harms of adding MTX to the IL17i compared to switching to IL12/23i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 41. In adult patients with active PsA despite treatment with an IL17i, what are the benefits and harms of adding MTX to the IL17i compared to switching to TNFi?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 42. In adult patients with active PsA despite treatment with an IL17i, what are the benefits and harms of switching to a different IL17i compared to switching to TNFi?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 43. In adult patients with active PsA despite treatment with an IL17i, what are the benefits and harms of switching to a different IL17i compared to switching to IL12/23i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 44. Among adults with active PsA, what are the benefits and harms of treat to target (or intensive therapy) compared to a not treat to target strategy (include liver toxicity, zoster, malignancy, infection, cardiovascular, IBD, uveitis)?

Summary: This PICO was directly addressed by one open label, multicenter RCT that compared tight control to standard therapy.[1] Methotrexate was the initial therapy for the tight control arm and followed by a specific treatment algorithm. Patients who did not achieve minimal disease activity (MDA) following 12 weeks of MTX (starting at 15 mg/week and ending at 25 mg/week) received combination therapy (MTX + sulfasalazine) for 8 weeks. Patients who still did not achieve MDA then received either combination treatment (MTX + cyclosporine or MTX + leflunomide) for 12 weeks if they had <3 swollen joints or first-line anti-TNFi therapy (usually etanercept unless contraindicated) for 12 weeks if they had ≥3 swollen joints. Patients who still did not achieve MDA and had ≥3 swollen joints then received second-line anti TNFi therapy for 12 weeks. Patients were seen every 4 weeks. At 48 weeks follow-up, statistically significant differences favoring tight control over standard therapy were reported for disease activity (measured by ACR 20 response) and skin (measured by PASI-75) in the evaluable patient population. Abdominal/GI discomfort occurred significantly more often in the MTX tight control group. Nausea was also more frequent in this group but the difference did not reach statistical significance. Liver enzyme abnormalities did not differ significantly between groups, but the effect size was imprecise due to a wide CI.

Quality of evidence across all critical outcomes: Low

Tight control compared to standard care for Adults with Active PsA

Bibliography: PICO 44: Tight Control versus Standard Care for Adults with Active PsA.

Quality assessment							Summary of findings			
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard care	With MTX tight control		Risk with standard care	Risk difference with MTX tight control
ACR20, 48 weeks											

Tight control compared to standard care for Adults with Active PsA

Bibliography: PICO 44: Tight Control versus Standard Care for Adults with Active PsA.

Quality assessment							Summary of findings				
173 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	37/84 (44.0%)	55/89 (61.8%)	**RR 1.40** (1.05 to 1.88) **Favors tight control**	440 per 1,000 (0.440)	**176 more per 1,000 (0.176)** (22 more to 388 more)
PASI75, 48 weeks											
156 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	27/81 (33.3%)	44/75 (58.7%)	**RR 1.76** (1.23 to 2.53) **Favors tight control**	333 per 1,000 (0.333)	**253 more per 1,000 (0.253)** (77 more to 510 more)
Liver enzyme abnormalities [c]											
206 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	28/105 (26.7%)	23/101 (22.8%)	**RR 0.85** (0.53 to 1.38)	267 per 1,000 (0.267)	**40 fewer per 1,000 (0.040)** (125 fewer to 101 more)
Abdominal/GI upset [d]											

Tight control compared to standard care for Adults with Active PsA

Bibliography: PICO 44: Tight Control versus Standard Care for Adults with Active PsA.

Quality assessment							Summary of findings				
206 (1 study)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	12/105 (11.4%)	31/101 (30.7%)	**RR 2.69** (1.46 to 4.93) **Favors standard care**	114 per 1,000 (0.114)	**193 more per 1,000 (0.193)** (53 more to 449 more)
Nausea											
206 (1 RCT)	serious [a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ LOW	27/105 (25.7%)	36/101 (35.6%)	**RR 1.39** (0.91 to 2.10)	257 per 1,000 (0.257)	**100 more per 1,000 (0.100)** (23 fewer to 283 more)

CI: Confidence interval; **RR:** Risk ratio

a. No blinding of patients/physicians. No patient data provided for primary outcome (ITT population); only OR presented in narrative. Recall bias for AEs described by authors as a limitation.
b. Wide CI that overlaps with line of no effect.
c. Cutoff for abnormal enzyme level was not defined in the study
d. Not defined in the study

Note: TICOPA trial. Additional limitations noted by authors included inability to test the efficacy of masked assessors; "blunting of the efficacy of tight control" since standard arm being treated by consultant rheumatologists at teaching hospitals and may already be following a more aggressive approach to treatment; possible dilution of intended treatment effect due to "deviations from the treatment escalation protocol."

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet. 2015;386(10012):2489-2498.

PICO 45. In adult patients with active axial PsA despite treatment with NSAIDs, what are the benefits and harms of switching to IL12/23i compared to switching to TNFi?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 46. In adult patients with active axial PsA despite treatment with NSAIDs, what are the benefits and harms of switching to IL17i compared to switching to TNFi?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 47. In adult patients with active axial PsA despite treatment with NSAIDs, what are the benefits and harms of switching to IL17i compared to switching to IL12/23i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 48. In adult patients with active PsA and predominant enthesitis who are both OSM and biologic treatment-naïve, what are the benefits and harms of starting OSM compared to starting NSAIDs?

Summary: This PICO was addressed indirectly by three double-blind RCTs comparing OSM to Placebo, all using apremilast.[1-3] No studies included a treatment arm of patients starting NSAIDs. The relevant outcomes measured included enthesitis, serious infection, liver toxicity, nausea and diarrhea. Because all trials had a placebo comparison and all (or almost all) patients had prior treatment with OSM and/or biologics, the indirectness of the evidence is very serious.

Only one of the apremilast studies [3] provided sufficient information to import into Table 1. The other [2] reported a non-significant trend toward greater improvement in MASES score in patients receiving apremilast compared with placebo; the magnitude of difference was smaller in this study. The apremilast groups had higher liver toxicity (non-significant difference with imprecision in the CI), but a statistically significant increase in GI intolerance compared to placebo.

Quality of evidence across all critical outcomes: Very low

Table 1. OSM or NSAIDs compared to placebo in patients with enthesitis who are treatment-naive

Bibliography: PICO 48: In patients with PsA and enthesitis who are treatment-naive, benefit/harm of starting OSM vs. starting NSAIDs.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With OSM		Risk with placebo	Risk difference with OSM
Enthesitis score (MASES) (LS mean change) – Apremilast vs. placebo											
326 (1 RCT)	not serious	serious [a]	very serious [b]	not serious	none	⨁◯◯◯ VERY LOW	165	161	-	The mean enthesitis score (MASES) (LS mean change) was **0**	MD **0.9 lower** (1.73 lower to 0.07 lower) **Favors apremilast**

Table 1. OSM or NSAIDs compared to placebo in patients with enthesitis who are treatment-naive

Bibliography: PICO 48: In patients with PsA and enthesitis who are treatment-naive, benefit/harm of starting OSM vs. starting NSAIDs.

Quality assessment							Summary of findings				
Nausea – TNFi vs. placebo											
259 (1 RCT)	not serious	not serious	very serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	5/113 (4.4%)	4/146 (2.7%)	**RR 0.62** (0.17 to 2.25)	44 per 1,000 (0.044)	**17 fewer per 1,000 (0.017)** (37 fewer to 55 more)
GI intolerance (diarrhea and nausea) – Apremilast vs. placebo											
983 (3 RCTs)	not serious	not serious	very serious [b]	not serious	none	⨁⨁◯◯ LOW	38/486 (7.8%)	162/497 (32.6%)	**RR 4.17** (3.00 to 5.80) **Favors placebo**	78 per 1,000 (0.078)	**248 more per 1,000 (0.248)** (156 more to 375 more)
Liver toxicity[d] – Apremilast vs. placebo											
984 (3 RCTs)	not serious	not serious	very serious [b]	not serious	none	⨁⨁◯◯ LOW	1/492 (0.2%)	6/492 (1.2%)	**RD 0.01** (-0.001 to 0.02) **Favors placebo**	2 per 1,000 (0.002)	**10 more per 1,000 (0.005)** (1 fewer to 20 more)

CI: Confidence interval; RD: Risk difference **RR:** Risk ratio

a. A second study, by Edwards et al 2016, reported a smaller improvement in enthesitis score but could not be added to RevMan. See discussion in summary paragraph.

b. Indirect comparison to placebo and all or almost all patients had prior exposure to OSMs or biologics.

c. Wide CI crossing significant effect and no-effect lines

d. Studies had slightly different cutoffs for abnormality: ALT > 150 u/l (2 studies), ALT >upper normal limit (1 study)

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Cutolo M, Myerson GE, Fleischmann RM, Liote F, Diaz-Gonzalez F, Van den Bosch F, et al. A Phase III, Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial. J Rheumatol. 2016;43(9):1724-1734.
2. Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Ann Rheum Dis. 2016;75(6):1065-1073.
3. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. J Rheumatol. 2015;42(3):479-488.

PICO 49. In adult patients with active PsA and predominant enthesitis despite treatment with OSM, what are the benefits and harms of switching to TNFi compared to switching to OSM?

Summary: This PICO was addressed indirectly by five double-blind RCTs (6 publications). Two studies (in three publications) involving PsA patients compared TNFi (golimumab and certolizumab pegol) to placebo.[1-3] Three studies compared OSM to Placebo, all using apremilast.[4-6] The relevant outcomes measured included enthesitis, serious infection, liver toxicity, nausea and diarrhea.

Enthesitis and adverse events could not be compared using adjusted indirect comparisons, so these findings are presented for drug versus placebo in Table 1. Only one of the apremilast studies [6] provided sufficient information to import into the comparison tables. The other [5] reported a non-significant trend toward greater improvement in MASES score in patients receiving apremilast compared with placebo; the magnitude of difference was smaller in this study. TNFis were superior to placebo in improving enthesitis. There was no significant difference between TNFi and placebo in serious infections, nausea and diarrhea, but all findings were imprecise. The apremilast groups had higher liver toxicity (non-significant difference with imprecision in the CI), but a statistically significant increase in GI intolerance.

Quality of evidence across all critical outcomes: Low

Table 1. TNFi or OSM compared to placebo in patients with enthesitis despite OSM
Bibliography: PICO 49: In patients with PsA and enthesitis despite OSM, benefit/harm of switching to TNFi compared to OSM.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With TNFi or OSM		Risk with placebo	Risk difference with TNFi or OSM
Enthesitis score (MASES) (LS mean change) – Apremilast vs. placebo											

Table 1. TNFi or OSM compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 49: In patients with PsA and enthesitis despite OSM, benefit/harm of switching to TNFi compared to OSM.

Quality assessment							Summary of findings				
326 (1 RCT)	not serious	serious [a]	serious [b]	Not serious	none	⨁⨁◯◯ LOW	165	161	-	The mean enthesitis score (MASES) (LS mean change) was **0**	MD **0.9 lower** (1.73 lower to 0.07 lower) **Favors apremilast**
Enthesitis, 14 weeks – Golimumab vs. placebo											
247 (1 RCT)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	75/105 (71.4%)	78/142 (54.9%)	**RR 0.77** (0.63 to 0.93) **Favors GOL**	714 per 1,000 (0.714)	**164 fewer per 1,000 (0.164)** (264 fewer to 50 fewer)
Serious infection – TNFi vs. placebo											
533 (2 RCTs)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	5/249 (2.0%)	3/284 (1.1%)	**RD -0.009** (-0.02 to 0.02)	20 per 1,000 (0.020)	**9 fewer per 1,000 (0.009)** (20 fewer to 20 more)
Diarrhea – TNFi vs. placebo											

Table 1. TNFi or OSM compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 49: In patients with PsA and enthesitis despite OSM, benefit/harm of switching to TNFi compared to OSM.

Quality assessment							Summary of findings				
259 (1 RCT)	not serious	not serious	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	4/113 (3.5%)	5/146 (3.4%)	**RR 0.97** (0.27 to 3.52)	35 per 1,000 (0.035)	**1 fewer per 1,000 (0.001)** (26 fewer to 89 more)
Nausea – TNFi vs. placebo											
259 (1 RCT)	not serious	not serious	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	5/113 (4.4%)	4/146 (2.7%)	**RR 0.62** (0.17 to 2.25)	44 per 1,000 (0.044)	**17 fewer per 1,000 (0.017)** (37 fewer to 55 more)
GI intolerance (diarrhea and nausea) – Apremilast vs. placebo											
983 (3 RCTs)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	38/486 (7.8%)	162/497 (32.6%)	**RR 4.17** (3.00 to 5.80) **Favors placebo**	78 per 1,000 (0.078)	**248 more per 1,000 (0.248)** (156 more to 375 more)
Liver toxicity[d] – Apremilast vs. placebo											
984 (3 RCTs)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	1/492 (0.2%)	6/492 (1.2%)	**RD 0.01** (-0.001 to 0.02) **Favors placebo**	2 per 1,000 (0.002)	**10 more per 1,000 (0.005)** (1 fewer to 20 more)

CI: Confidence interval; RD: Risk difference **RR:** Risk ratio

a. A second study, by Edwards et al 2016, reported a smaller improvement in enthesitis score but could not be added to RevMan. See discussion in summary paragraph.
b. Indirect comparison to placebo
c. Wide CI crossing significant effect and no-effect lines
d. Studies had slightly different cutoffs for abnormality: ALT > 150 u/l (2 studies), ALT >upper normal limit (1 study)

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60(4):976-986.
2. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73(1):48-55.
3. Gladman D, Fleischmann R, Coteur G, Woltering F, Mease PJ. Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. Arthritis Care Res (Hoboken). 2014;66(7):1085-1092.
4. Cutolo M, Myerson GE, Fleischmann RM, Liote F, Diaz-Gonzalez F, Van den Bosch F, et al. A Phase III, Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial. J Rheumatol. 2016;43(9):1724-1734.
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PICO 50. In adult patients with active PsA and predominant enthesitis despite treatment with OSM, what are the benefits and harms of switching to OSM compared to switching to IL12/23i?

Summary: This question was indirectly addressed using 5 placebo-controlled RCTs (6 publications).[1-6] Apremilast was the only OSM with data suitable for this question. Two RCTs comparing ustekinumab versus placebo[1,2] and three studies comparing apremilast versus placebo[3-6] were included. None of the studies stratified outcomes by history of OSM use, which adds another layer of indirectness. However, the majority of patients in these studies had a history of OSM use, usually methotrexate.

Enthesitis and adverse events could not be compared using adjusted indirect comparisons, so these findings are presented for drug versus placebo in Table 1. Enthesitis scores (MASES) were provided by both ustekinumab studies and two of the three apremilast studies. Only one of the apremilast studies[4] provided sufficient information to import into the comparison tables. The other[6] reported a non-significant trend toward greater improvement in MASES score in patients receiving apremilast compared with placebo; the magnitude of difference was smaller than was reported by Kavanaugh et al.[4] Ustekinumab was superior to placebo for reducing the number of patients with MASES score >1. The apremilast groups had higher liver toxicity (non-significant difference with imprecision in the CI), but a statistically significant increase in GI intolerance. Serious infection rates did not differ significantly between ustekinumab and placebo groups.

Quality of evidence across all critical outcomes: Low

Table 1. OSM or IL12/23i compared to placebo in patients with enthesitis despite OSM
Bibliography: PICO 50: In patients with PsA and enthesitis despite OSM, benefit/harm of switching to OSM compared to IL12/23i.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With OSM or IL12/23i		Risk with placebo	Risk difference with OSM or IL12/23i
Enthesitis score (MASES) (LS mean change) – Apremilast vs. placebo											

Table 1. OSM or IL12/23i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 50: In patients with PsA and enthesitis despite OSM, benefit/harm of switching to OSM compared to IL12/23i.

Quality assessment							Summary of findings				
326 (1 RCT)	not serious	serious [a]	serious [b]	Not serious	none	⨁⨁◯◯ LOW	165	161	-	The mean enthesitis score (MASES) (LS mean change) was **0**	MD **0.9 lower** (1.73 lower to 0.07 lower)
Enthesitis (MASES score >1) – Ustekinumab vs. placebo											
633 (2 RCTs)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	171/205 (83.4%)	288/428 (67.3%)	**RR 0.81** (0.74 to 0.88) **Favors IL12/23i**	834 per 1,000 (0.834)	**158 fewer per 1,000 (0.158)** (217 fewer to 100 fewer)
Serious infection – Ustekinumab vs. placebo											
925 (2 RCTs)	not serious	serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	2/309 (0.6%)	4/616 (0.6%)	**RR 0.84** (0.20 to 3.50) **No difference**	6 per 1,000 (0.006)	**1 fewer per 1,000** (5 fewer to 15 more)
GI intolerance (diarrhea and nausea) – Apremilast vs. placebo											

Table 1. OSM or IL12/23i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 50: In patients with PsA and enthesitis despite OSM, benefit/harm of switching to OSM compared to IL12/23i.

Quality assessment							Summary of findings				
983 (3 RCTs)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	38/486 (7.8%)	162/497 (32.6%)	**RR 4.17** (3.00 to 5.80) **Favors placebo**	78 per 1,000 (0.078)	**248 more per 1,000 (0.248)** (156 more to 375 more)
Liver toxicity[d] – Apremilast vs. placebo											
984 (3 RCTs)	not serious	not serious	serious [b]	serious [c]	none	⨁⨁◯◯ LOW	1/492 (0.2%)	6/492 (1.2%)	**RR 3.32** (0.67 to 16.35)	2 per 1,000 (0.002)	**5 more per 1,000 (0.005)** (1 fewer to 31 more)

CI: Confidence interval; **RR:** Risk ratio

a. A second study, by Edwards et al 2016, reported a smaller improvement in enthesitis score but could not be imported to RevMan. See discussion in summary paragraph.

b. Indirect comparison to placebo

c. Wide CI crossing significant effect and no-effect lines

d. Studies had slightly different cutoffs for abnormality: ALT > 150 u/l (2 studies), ALT >upper normal limit (1 study)

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

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5. Cutolo M, Myerson GE, Fleischmann RM, Liote F, Diaz-Gonzalez F, Van den Bosch F, et al. A Phase III, Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial. J Rheumatol. 2016;43(9):1724-1734.
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PICO 51. In adult patients with active PsA and predominant enthesitis despite treatment with OSM, what are the benefits and harms of switching to OSM compared to switching to IL-17i?

Summary: This question was indirectly addressed using 7 placebo-controlled RCTs (in 8 publications).[1-8] Apremilast was the only OSM with data suitable for this question. In all, four RCTs comparing IL17i (ixekizumab, secukinumab and brodalumab)[1-4] versus placebo and three studies comparing apremilast versus placebo[5-8] were included. None of the studies stratified outcomes by history of OSM use, which adds another layer of indirectness. However, the majority of patients in these studies had a history of OSM use, usually methotrexate.

Enthesitis and adverse events could not be compared using adjusted indirect comparisons, so these findings are presented for drug versus placebo in Table 1. Enthesitis scores (MASES) were provided by two of the three apremilast studies. Only one of the apremilast studies[6] provided sufficient information to import into the comparison tables. The other[8] reported a non-significant trend toward greater improvement in MASES score in patients receiving apremilast compared with placebo; the magnitude of difference was smaller than was reported by Kavanaugh et al.[6] IL17i was superior to placebo for increasing the number of patients with enthesitis resolution. Two IL17i studies compared mean change in Leeds Enthesitis Index score in drug vs. placebo. One trial found a significant benefit of ixekizumab over placebo, while the other trial found no significant difference in change score between brodalumab and placebo (the estimate was imprecise). The apremilast groups had higher liver toxicity (non-significant difference with imprecision in the CI), but a statistically significant increase in GI intolerance. Rates of serious infection did not differ significantly between IL17i and placebo groups, but the effect size was imprecise.

Quality of evidence across all critical outcomes: Low

Table 1. OSM or IL17i compared to placebo in patients with enthesitis despite OSM
Bibliography: In patients with PsA and enthesitis despite OSM, benefit/harm of switching to IL17i compared to OSM.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With OSM or IL17i		Risk with placebo	Risk difference with OSM or IL17i
Enthesitis score (MASES) (LS mean change) – Apremilast vs. placebo											

Table 1. OSM or IL17i compared to placebo in patients with enthesitis despite OSM

Bibliography: In patients with PsA and enthesitis despite OSM, benefit/harm of switching to IL17i compared to OSM.

Quality assessment							Summary of findings				
326 (1 RCT)	not serious	serious [a]	serious [b]	not serious	none	⨁⨁◯◯ LOW	165	161	-	-	MD **0.9 lower** (1.73 lower to 0.07 lower)
Enthesitis Resolution – IL17i vs. placebo											
822 (3 RCTs)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	58/284 (20.4%)	242/538 (45.0%)	**RR 2.33** (1.80 to 3.02) **Favors IL17i**	204 per 1,000 (0.204)	**272 more per 1,000 (0.272)** (163 more to 413 more)
Enthesitis score (Leeds Enthesitis Index) – Ixekizumab vs. placebo											
197 (1 RCT)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	102	95	-	-	MD **0.7 lower** (1.37 lower to 0.03 lower)
Enthesitis score (Leeds Enthesitis Index) – Brodalumab vs. placebo											
112 (1 RCT)	not serious	not serious	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	55	57	-	-	MD **0.1 lower** (1.06 lower to 0.86 higher)

Table 1. OSM or IL17i compared to placebo in patients with enthesitis despite OSM

Bibliography: In patients with PsA and enthesitis despite OSM, benefit/harm of switching to IL17i compared to OSM.

Quality assessment							Summary of findings				
Serious infection – IL17i vs. placebo											
1189 (3 RCTs)	not serious	not serious	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	5/406 (1.2%)	18/685 (2.6%)	**RR 1.79** (0.75 to 4.30)	12 per 1,000 (0.012)	**9 more per 1,000 (0.009)** (3 fewer to 52 more)
GI intolerance (diarrhea and nausea) – Apremilast vs. placebo											
983 (3 RCTs)	not serious	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	38/486 (7.8%)	162/497 (32.6%)	**RR 4.17** (3.00 to 5.80) **Favors placebo**	78 per 1,000 (0.078)	**248 more per 1,000 (0.248)** (156 more to 375 more)
Liver toxicity[e] – Apremilast vs. placebo											
984 (3 RCTs)	not serious	not serious	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	1/492 (0.2%)	6/492 (1.2%)	**RR 3.32** (0.67 to 16.35)	2 per 1,000 (0.002)	**5 more per 1,000 (0.005)** (1 fewer to 31 more)

CI: Confidence interval; **RR:** Risk ratio

a. A second study, by Edwards et al 2016, reported a smaller improvement in enthesitis score but could not be imported to RevMan. See discussion in summary paragraph.

b. Indirect comparison to placebo

c. Substantial heterogeneity between secukinumab studies.

d. Wide CI crossing significant effect and no-effect lines

e. Studies had slightly different cutoffs for abnormality: ALT > 150 u/l (2 studies), ALT >upper normal limit (1 study)

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386(9999):1137-1146.
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6. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014;73(6):1020-1026.
7. Cutolo M, Myerson GE, Fleischmann RM, Liote F, Diaz-Gonzalez F, Van den Bosch F, et al. A Phase III, Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial. J Rheumatol. 2016;43(9):1724-1734.
8. Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Ann Rheum Dis. 2016;75(6):1065-1073.

PICO 52. In adult patients with active PsA and predominant enthesitis despite treatment with OSM, what are the benefits and harms of switching to TNFi compared to switching to IL12/23i?

Summary: This PICO was indirectly addressed by 4 studies (5 publications).[1-5] Two RCTs (3 publications) compared TNFis with placebo,[1-3] while two RCTs compared ustekinumab with placebo.[4,5]

Enthesitis and adverse events could not be compared using adjusted indirect comparisons, so these findings are presented for drug versus placebo in Table 1. Both ustekinumab and golimumab were superior to placebo in reducing the number of patients with enthesitis or the number of patients with severe enthesitis. There was no significant difference between TNFi and placebo in serious infections, nausea and diarrhea, but all findings were imprecise. Ustekinumab showed no significant difference with placebo in rate of serious infections.

Quality of evidence across all critical outcomes: Low

Table 1. TNFi or IL12/23i compared to placebo in patients with enthesitis despite OSM
Bibliography: PICO 52: TNFi compared to IL12/23i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With TNFi or IL12/23i		Risk with placebo	Risk difference with TNFi or IL12/23i
Enthesitis (MASES) score >1 – Ustekinumab vs. placebo											
633 (2 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	171/205 (83.4%)	288/428 (67.3%)	**RR 0.81** (0.74 to 0.88) **Favors IL12/23i**	834 per 1,000 (0.834)	**158 fewer per 1,000 (0.158)** (217 fewer to 100 fewer)
Enthesitis, 14 weeks – Golimumab vs. placebo											

Table 1. TNFi or IL12/23i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 52: TNFi compared to IL12/23i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
247 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	75/105 (71.4%)	78/142 (54.9%)	**RR 0.77** (0.63 to 0.93) **Favors GOL**	714 per 1,000 (0.714)	**164 fewer per 1,000 (0.164)** (264 fewer to 50 fewer)
Serious infection – Ustekinumab vs. placebo											
925 (2 RCTs)	not serious	serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	2/309 (0.6%)	4/616 (0.6%)	**RR 0.84** (0.20 to 3.50) **No difference**	6 per 1,000 (0.006)	**1 fewer per 1,000** (5 fewer to 15 more)
Serious infection – TNFi vs. placebo											
533 (2 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/249 (2.0%)	3/284 (1.1%)	**RR 0.55** (0.11 to 2.77)	20 per 1,000 (0.020)	**9 fewer per 1,000 (0.009)** (18 fewer to 36 more)
Diarrhea – TNFi vs. placebo											

Table 1. TNFi or IL12/23i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 52: TNFi compared to IL12/23i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
259 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	4/113 (3.5%)	5/146 (3.4%)	**RR 0.97** (0.27 to 3.52)	35 per 1,000 (0.035)	**1 fewer per 1,000 (0.001)** (26 fewer to 89 more)
Nausea – TNFi vs. placebo											
259 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/113 (4.4%)	4/146 (2.7%)	**RR 0.62** (0.17 to 2.25)	44 per 1,000 (0.044)	**17 fewer per 1,000 (0.017)** (37 fewer to 55 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison to placebo

b. Wide CI crossing significant effect and no-effect lines

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60(4):976-986.

2. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73(1):48-55.
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PICO 53. In adult patients with active PsA and predominant enthesitis despite treatment with OSM, what are the benefits and harms of switching to TNFi compared to switching to IL17i?

Summary: This PICO was addressed indirectly by 5 double-blind RCTs (6 publications) involving PsA patients or psoriasis patients comparing either TNFi or IL17i to placebo.[1-6] The relevant outcomes included enthesitis resolution, Leeds enthesitis index change from baseline, and adverse events. All drugs showed statistically significant improvements in enthesitis resolution over placebo.

Since both TNFi and IL17i studies reported enthesitis resolution, we compared the findings for this outcome between drug classes using adjusted indirect comparisons (Table 1). Golimumab was the only TNFi with a study that reported this outcome. The comparison found no significant difference between golimumab and IL17i (secukinumab and ixekizumab) but was imprecise due to a wide CI that overlapped the line of no effect.

Adverse events are presented for drug versus placebo in Table 2. Both IL17i and golimumab were superior to placebo in reducing the number of patients with enthesitis. Two IL17i studies compared mean change in Leeds Enthesitis Index score in drug vs. placebo. One trial found a significant benefit of ixekizumab over placebo, while the other trial found no significant difference in change score between brodalumab and placebo (the estimate was imprecise). There was no significant difference between TNFi and placebo in serious infections, nausea and diarrhea, but all findings were imprecise. IL17i showed no significant difference with placebo in rate of serious infections.

Quality of evidence across all critical outcomes: Low

Table 1. TNFi compared to IL17i for patients with active PsA and predominant enthesitis despite OSM

Bibliography: PICO 53: TNFi compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							IL17i	TNFi		Risk with IL17i	Risk difference with TNFi
Enthesitis resolution, Bucher adjusted indirect comparison											

Table 1. TNFi compared to IL17i for patients with active PsA and predominant enthesitis despite OSM

Bibliography: PICO 53: TNFi compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
1069 (4 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	GOL	**RR 0.71** (0.39 to 1.30)	450 per 1,000 (0.450)	**130 fewer per 1000 (0.130)** (274 fewer to 135 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only one trial had 100% patients with prior OSM exposure, most had 50-83% of patients with prior OSM exposure.

b. Wide 95% CI

Table 2. TNFi or IL17i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 53: TNFi compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With TNFi or IL17i**		**Risk with placebo**	**Risk difference with TNFi or IL17i**
Enthesitis Resolution – IL17i vs. placebo											

Table 2. TNFi or IL17i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 53: TNFi compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
822 (3 RCTs)	not serious	not serious	serious [1]	not serious	none	⨁⨁⨁◯ MODERATE	58/284 (20.4%)	242/538 (45.0%)	**RR 2.23** (1.36 to 3.66) **Favors IL17i**	204 per 1,000 (0.204)	**251 more per 1,000 (0.251)** (74 more to 543 more)
Enthesitis, 14 weeks – Golimumab vs. placebo											
247 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	75/105 (71.4%)	78/142 (54.9%)	**RR 0.77** (0.63 to 0.93) **Favors GOL**	714 per 1,000 (0.714)	**164 fewer per 1,000 (0.164)** (264 fewer to 50 fewer)
Enthesitis score (Leeds Enthesitis Index) – Ixekizumab vs. placebo											
197 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	102	95	-	-	MD **0.7 lower** (1.37 lower to 0.03 lower)
Enthesitis score (Leeds Enthesitis Index) – Brodalumab vs. placebo											
112 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	55	57	-	-	MD **0.1 lower** (1.06 lower to 0.86 higher)

Table 2. TNFi or IL17i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 53: TNFi compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
Serious infection – IL17i vs. placebo											
1189 (3 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/406 (1.2%)	18/685 (2.6%)	**RR 1.79** (0.75 to 4.30)	12 per 1,000 (0.012)	**9 more per 1,000 (0.009)** (3 fewer to 52 more)
Serious infection – TNFi vs. placebo											
533 (2 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/249 (2.0%)	3/284 (1.1%)	**RR 0.55** (0.11 to 2.77)	20 per 1,000 (0.020)	**9 fewer per 1,000 (0.009)** (18 fewer to 36 more)
Diarrhea – TNFi vs. placebo											
259 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	4/113 (3.5%)	5/146 (3.4%)	**RR 0.97** (0.27 to 3.52)	35 per 1,000 (0.035)	**1 fewer per 1,000 (0.001)** (26 fewer to 89 more)
Nausea – TNFi vs. placebo											
259 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/113 (4.4%)	4/146 (2.7%)	**RR 0.62** (0.17 to 2.25)	44 per 1,000 (0.44)	**17 fewer per 1,000 (0.017)** (37 fewer to 55 more)

CI: Confidence interval; **RR:** Risk ratio
a. Indirect comparison to placebo
b. Wide CI crossing significant effect and no-effect lines

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 54. In adult patients with active PsA and predominant enthesitis despite treatment with OSM, what are the benefits and harms of switching to IL12/23i compared to switching to IL17i?

Summary: This PICO was addressed indirectly by 7 double-blind RCTs comparing either IL12/23i or IL17i to placebo in patients with PsA.[1-7] The relevant outcomes included enthesitis resolution, enthesitis (MASES) score >1, Leeds Enthesitis Index change from baseline, and adverse events.

Infection was the only relevant outcome that was comparable between IL12/23i studies and IL17i studies, so we compared infection rates between drug classes using adjusted indirect comparisons for various outcomes (Table 1). No significant between-class difference was identified, but the effect estimate had serious imprecision due to a wide CI that overlapped the line of no effect.

Enthesitis findings could not be compared using adjusted indirect comparisons because of differences in measurement between the drug classes, so these findings are presented for drug versus placebo in Table 2. IL17i and ustekinumab were superior to placebo in enthesitis resolution and reducing the number of patients with enthesitis and a MASES score >1, respectively. Two IL17i studies also compared mean change in Leeds Enthesitis Index score in drug vs. placebo. One trial found a significant benefit of ixekizumab over placebo, while the other trial found no significant difference in change score between brodalumab and placebo (the estimate was imprecise). Serious infection rates were so low for IL17i and ustekinumab that adjusted indirect comparison was not performed. Neither drug class showed significantly different serious infection rates compared to placebo groups, but the findings were imprecise for IL17i due to wide 95% confidence intervals.

Quality of evidence across all critical outcomes: Moderate

Table 1. IL12/23i compared to IL17i for patients with active PsA and predominant enthesitis despite OSM

Bibliography: PICO 54: IL12/23i compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							IL12/23i	IL17i		Risk with IL12/23i	Risk difference with IL17i
Infection											

Table 1. IL12/23i compared to IL17i for patients with active PsA and predominant enthesitis despite OSM

Bibliography: PICO 54: IL12/23i compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
1527 (4 RCTs)	Not serious	Not serious	Not serious[a]	Serious[b]	None	⊕⊕⊕◯ MODERATE	IL12/23i	IL17i	**RR 1.26** (0.81 to 1.97)	211 per 1,000 (0.211)	**55 more per 1000 (0.055)** (40 fewer to 205 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-83% of patients had prior OSM exposure in most trials, but patient characteristics and prior drug exposure are similar between drug classes.

b. Wide 95% CI

Table 2. IL12/23i or IL17i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 54: IL12/23i compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With IL12/23i or IL17i**		**Risk with placebo**	**Risk difference with IL12/23i or IL17i**
Enthesitis Resolution – IL17i vs. placebo											

Table 2. IL12/23i or IL17i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 54: IL12/23i compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
822 (3 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	58/284 (20.4%)	242/538 (45.0%)	**RR 2.23** (1.36 to 3.66) **Favors IL17i**	204 per 1,000 (0.204)	**251 more per 1,000 (0.251)** (74 more to 543 more)
Enthesitis score (Leeds Enthesitis Index) – Ixekizumab vs. placebo											
197 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	102	95	-	-	MD **0.7 lower** (1.37 lower to 0.03 lower)
Enthesitis score (Leeds Enthesitis Index) – Brodalumab vs. placebo											
112 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	55	57	-	-	MD **0.1 lower** (1.06 lower to 0.86 higher)
Enthesitis (MASES) score >1 – Ustekinumab vs. placebo											
633 (2 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	171/205 (83.4%)	288/428 (67.3%)	**RR 0.81** (0.74 to 0.88) **Favors IL12/23i**	834 per 1,000 (0.834)	**158 fewer per 1,000 (0.158)** (217 fewer to 100 fewer)

Table 2. IL12/23i or IL17i compared to placebo in patients with enthesitis despite OSM

Bibliography: PICO 54: IL12/23i compared to IL17i for patients with active PsA and enthesitis despite OSM

Quality assessment							Summary of findings				
Serious infection – IL17i vs. placebo											
1189 (3 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/406 (1.2%)	18/685 (2.6%)	**RR 1.79** (0.75 to 4.30)	12 per 1,000 (0.012)	**9 more per 1,000 (0.009)** (3 fewer to 52 more)
Serious infection – Ustekinumab vs. placebo											
925 (2 RCTs)	not serious	serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	2/309 (0.6%)	4/616 (0.6%)	**RR 0.84** (0.20 to 3.50) **No difference**	6 per 1,000 (0.006)	**1 fewer per 1,000** (5 fewer to 15 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison to placebo

b. Wide 95% CI that crosses line of no effect

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

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PICO 55. In adult patients with active PsA and predominant enthesitis despite treatment with NSAIDs, what are the benefits and harms of switching to tofacitinib compared to switching to OSM?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

Special Populations

PICO 56: In patients with active PsA, what are the benefits and harms of vaccination with killed vaccines prior to starting biologic compared to vaccination while using a biologic?

Summary: Only one study directly addressed this PICO question[1] This was an RCT comparing the antibody response of patients with PsA randomized to etanercept or placebo and subsequently vaccinated with a 23-valent pneumococcal vaccine. Table 1 shows that the percentage of patients with 2-fold or 4-fold increase in antibody titers to five different antigens did not differ significantly between groups, but the 95% CIs showed serious imprecision in all effect estimates.

Adverse events were indirectly addressed by six studies evaluating vaccination safety in patients (mostly with rheumatoid arthritis) treated with TNFi.[2-7] All of the studies evaluated adverse events and serious adverse events in patients vaccinated during treatment with TNFi or Placebo. No significant difference was found in all studies between TNFi and Placebo patients. In one study, even though there were no cases reported in the category of tuberculosis (TB) in either group during the RCT, 2 cases (0.9%) were reported during the open-label extension (OLE) after CZP treatment, among which one was considered related to study drug by the investigator. In the same study, serious adverse events occurred at a rate of 1.8% in the CZP group during the RCT period, and in 6.8% of CZP-treated patients overall (combined RCT and OLE), which might be attributable to both longer duration and the OLE period. In another study, the rate of infectious adverse events was statistically significantly higher in the placebo treatment group [23.5% (27/115)] versus the adalimumab group [12.6% (14/111)] (p = 0.039).

Quality of evidence across all critical outcomes: Low

Table 1. Antibody Response in Patients Who Received Etanercept or Placebo Prior to Vaccination with Pneumococcal Vaccine

Bibliography: Etanercept versus Placebo for PV vaccinated patients.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With ETN		Risk with Placebo	Risk difference with ETN
2-fold increase in titer 9V											

Table 1. Antibody Response in Patients Who Received Etanercept or Placebo Prior to Vaccination with Pneumococcal Vaccine

Bibliography: Etanercept versus Placebo for PV vaccinated patients.

Quality assessment							Summary of findings				
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	53/90 (58.9%)	47/94 (50.0%)	**OR 0.70** (0.39 to 1.25)	589 per 1,000	**88 fewer per 1,000** (230 fewer to 53 more)
2-fold increase in titer 14											
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	50/90 (55.6%)	55/94 (58.5%)	**OR 1.13** (0.63 to 2.02)	556 per 1,000	**30 more per 1,000** (115 fewer to 161 more)
2-fold increase in titer 18C											
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	56/90 (62.2%)	58/94 (61.7%)	**OR 0.98** (0.54 to 1.77)	622 per 1,000	**5 fewer per 1,000** (151 fewer to 122 more)
2-fold increase in titer 19F											
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	36/90 (40.0%)	33/94 (35.1%)	**OR 0.81** (0.45 to 1.48)	400 per 1,000	**49 fewer per 1,000** (169 fewer to 97 more)
2-fold increase in titer 23F											

Table 1. Antibody Response in Patients Who Received Etanercept or Placebo Prior to Vaccination with Pneumococcal Vaccine

Bibliography: Etanercept versus Placebo for PV vaccinated patients.

Quality assessment							Summary of findings				
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	52/90 (57.8%)	48/94 (51.1%)	**OR 0.76** (0.43 to 1.36)	578 per 1,000	**68 fewer per 1,000** (207 fewer to 73 more)
4-fold increase of titer 9V											
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	41/90 (45.6%)	32/94 (34.0%)	**OR 0.62** (0.34 to 1.12)	456 per 1,000	**114 fewer per 1,000** (234 fewer to 28 more)
4-fold increase in titer 14											
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	41/90 (45.6%)	40/94 (42.6%)	**OR 0.89** (0.49 to 1.59)	456 per 1,000	**29 fewer per 1,000** (165 fewer to 115 more)
4-fold increase in titer 18C											
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⊕⊕◯◯ LOW	42/90 (46.7%)	38/94 (40.4%)	**OR 0.78** (0.43 to 1.39)	467 per 1,000	**61 fewer per 1,000** (193 fewer to 82 more)
4-fold increase in titer 19F											

Table 1. Antibody Response in Patients Who Received Etanercept or Placebo Prior to Vaccination with Pneumococcal Vaccine

Bibliography: Etanercept versus Placebo for PV vaccinated patients.

Quality assessment							Summary of findings				
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	20/90 (22.2%)	18/94 (19.1%)	**OR 0.83** (0.41 to 1.69)	222 per 1,000	**31 fewer per 1,000** (117 fewer to 103 more)
4-fold increase in titer 23F											
184 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	31/90 (34.4%)	25/94 (26.6%)	**OR 0.69** (0.37 to 1.30)	344 per 1,000	**78 fewer per 1,000** (182 fewer to 61 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Outcomes not direct and only a single vaccine is used, which may not be representative of the immune response to other vaccines

b. Wide CI crossing significant effect and no-effect lines

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Ribeiro, 2013	Cohort study	21 days	99 Patients with RA	Influenza A/H1N1 killed virus vaccine given to 11 pts with Abatacept (RA-ABA), 33 MTX (RA-MTX) and 55 healthy controls	The rates of minor side effects were comparable: 55% in RA-ABA patients, 39% in RA-MTX patients, and 40% in control groups (P=0.64). Severe side effects were not reported during the followup period.
Migita, 2015	Randomized, double-blind placebo-controlled study	6 weeks	703 patients with RA	PPSV23 administered to 353 patients on MTX, ABA, other biologics, or controls	There were no reported adverse events associated with PPSV23 vaccination.
Kivitz A, 2014	Single-blind Randomized placebo-controlled	6-week	224 patients with RA	Pneumococcal (polysaccharide 23) and influenza vaccines administered at Week 2 to 110 patients with CZP and 114 with	AE occurred 62.3% in placebo and 63.6% CZP groups. Serious AE occurred in 1 patient (0.9%) in the placebo group, and in 2 patients (1.8%) in the CZP group. Serious AE occurred in 6.8% of

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	trial			Placebo	CZP-treated patients overall (combined RCT and OLE). Even though there were no cases reported in the category of tuberculosis (TB) in either group during the RCT, 2 cases (0.9%) were reported during the OLE after CZP treatment, among which one was considered related to study drug by the investigator
Franca I, 2012	Cohort study	21 days	236 pts with RA, SpA and PsA, and 117 healthy controls	anti-influenza A H1N1/2009 vaccine administered to 120 pts on anti-TNF agents, 116 inflammatory arthritis patients on DMARDs, and 117 healthy controls.	Only mild systemic reactions were more often observed in patients on anti-TNF compared with healthy controls: fever (8.3% vs 0.9%, P = 0.01), arthralgia (12.5% vs 4.3%, P = 0.03), and nasal congestion (13.3% vs 4.3%, P = 0.014). No severe adverse event was reported in any group.
Elkayam O, 2008	Cohort study	4 to 6 weeks	43 RA patients and 18 AS patients	Split-virion inactivated vaccine containing15g hemagglutinin/dose of each of A/New Caledionan/20/1999 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 (M) was given to 22 pts on the day of administration of infliximab, while 16 received the vaccine 3 weeks after infliximab.	No adverse effects other than injection site pain were recorded.
Kaine J, 2007	Double-blind, randomized trial	4 weeks	208 adult patients with RA	Pneumococcal and influenza vaccines were administered on Day 8 to patients who received adalimumab (99) or placebo (109).	During the blinded period of the study no deaths were reported, and one patient receiving placebo reported a serious AE. A slightly greater percentage of patients in the placebo group reported an AE than did patients in the adalimumab group [54.8% (63/115) vs 45.9% (51/111), respectively]. The most frequently reported treatment-emergent AE occurring during the blinded period of the study were upper respiratory tract infection and injection site reaction; both were reported more frequently by placebo-treated patients. There were no serious infectious AE, malignancies, or opportunistic infections, including tuberculosis, reported during the double-blind period. The rate of infectious AE was statistically significantly higher in the placebo treatment group [23.5% (27/115)] versus the adalimumab group [12.6% (14/111)] (p = 0.039).

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PICO 57. In patients with active PsA, what are the benefits and harms of vaccination with live attenuated vaccines prior to starting biologic compared to vaccination while using a biologic?

Summary: The literature searches identified one large retrospective cohort study of patients with immune-mediated diseases who received the Herpes Zoster vaccine that addressed this PICO question.[1] As a retrospective observational study the GRADE rating started at low; since only 3% of patients had PsA (the rest had psoriasis, ankylosing spondylitis, rheumatoid arthritis, and inflammatory bowel disease); the rating was further downgraded to very low due to indirectness of the patient population. The Herpes Zoster incidence rate was similar in patients who received biologics and patients who did not receive biologics (see table below).

Quality of evidence across all critical outcomes: Very low

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results		
						HZ cases	HZ incidence rate
Zhang et al. 2012	Retrospective cohort study	2 years	463,541 patients over 60 with RA, psoriasis, psoriatic arthritis, ankylosing spondylitis, and/or IBD	Herpes Zoster vaccine given to pts with TNFi and non-TNFi biologics, DMARDs, and oral glucocorticoids	Overall Medications (mutually exclusive groups):	138	6.7 (5.7-7.9)
					Biologics (regardless of concomitant DMARDs or oral glucocorticoids)	14	8.5(5.1-14.4)
					Anti-TNF therapies	12	8.5(4.8-15.0)
					DMARDs (without biologics but regardless of oral glucocorticoids)	25	7.0(4.7-10.3)
					Oral glucocorticoids alone	21	10.3(6.7-15.8)

References

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Comorbidities

PICO 58. In adult patients with active PsA and IBD despite treatment with an OSM, what are the benefits and harms of switching to TNFi (monoclonal antibodies [MABs]) vs. switching to TNFi soluble receptor biologic (i.e. etanercept)?

Summary: The literature searches did not identify any direct studies that addressed this PICO question. Two systematic reviews compared TNFi (monoclonal antibodies [MABs]) to placebo, one in Crohn's Disease patients,[1] and another in Ulcerative Colitis patients.[2] One RCT compared etanercept with Placebo in patients with Crohn's Disease.[3] The systematic reviews revealed that anti-TNF MABs result in a 1.66-fold higher likelihood of induction of remission (95% CI: 1.17–2.36) and 1.43-fold higher likelihood of induction of response (95% CI: 1.17–1.73) compared to placebo in patients with Crohn's Disease. For patients with ulcerative colitis, meta-analyses found a 2.45-fold higher likelihood of induction of remission and 1.65-fold higher likelihood of induction of response compared to placebo (RR: 2.45, 95% CI: 1.72–3.47 and RR: 1.65, 95% CI: 1.37–1.99 respectively). In the RCT the rates of clinical response at week 2, 4 and 8 were similar in patients treated with etanercept compared with placebo, RR=1.91 (0.8-4.75), 0.87 (0.43-1.76), and 1.01 (0.41-2.52) respectively.

Quality of evidence across all critical outcomes: Moderate

TNFi (MAB) compared to Placebo for Crohn's disease

Bibliography: TNFi (MAB) compared to Placebo for Crohn's disease

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With TNFi (MAB)**		**Risk with Placebo**	**Risk difference with TNFi (MAB)**
Induction of remission endpoint											
1771 (6 RCTs)	not serious	not serious	serious [a]	not serious	none	⊕⊕⊕◯ MODERATE	150/882 (17.0%)	227/889 (25.5%)	**RR 1.66** (1.17 to 2.36)	170 per 1,000	**112 more per 1,000** (29 more to 231 more)
Induction of response endpoint											
1771 (6 RCTs)	not serious	not serious	serious [a]	not serious	none	⊕⊕⊕◯ MODERATE	246/882 (27.9%)	346/889 (38.9%)	**RR 1.43** (1.17 to 1.73)	279 per 1,000	**120 more per 1,000** (47 more to 204 more)
Maintenance of remission endpoint											
1690 (5 RCTs)	not serious	not serious	serious [a]	not serious	none	⊕⊕⊕◯ MODERATE	153/839 (18.2%)	278/851 (32.7%)	**RR 1.78** (1.51 to 2.09)	182 per 1,000	**142 more per 1,000** (93 more to 199 more)
Maintenance of response endpoint											

1467 (4 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	184/729 (25.2%)	315/738 (42.7%)	**RR 1.68** (1.46 to 1.93)	252 per 1,000	**172 more per 1,000** (116 more to 235 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Indirect comparison to placebo

TNFi (MAB) compared to Placebo for Ulcerative colitis

Bibliography: TNFi (MAB) compared to Placebo for Ulcerative colitis

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With TNFi (MAB)**		**Risk with Placebo**	**Risk difference with TNFi (MAB)**
Induction of remission endpoints											
1823 (6 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	82/912 (9.0%)	210/911 (23.1%)	**RR 2.45** (1.72 to 3.47)	90 per 1,000	**130 more per 1,000** (65 more to 222 more)
Induction of response endpoint											
1780 (5 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	300/892 (33.6%)	491/888 (55.3%)	**RR 1.65** (1.37 to 1.99)	336 per 1,000	**219 more per 1,000** (124 more to 333 more)

TNFi (MAB) compared to Placebo for Ulcerative colitis

Bibliography: TNFi (MAB) compared to Placebo for Ulcerative colitis

Quality assessment							Summary of findings				
Maintenance of remission endpoint											
1070 (3 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	65/537 (12.1%)	129/533 (24.2%)	**RR 2.00** (1.52 to 2.62)	121 per 1,000	**121 more per 1,000** (63 more to 196 more)
Maintenance of response endpoint											
1070 (3 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	118/537 (22.0%)	208/533 (39.0%)	**RR 1.76** (1.46 to 2.14)	220 per 1,000	**167 more per 1,000** (101 more to 251 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Indirect comparison to placebo

Etanercept compared to Placebo for Crohn's Disease

Bibliography: Etanercept compared to Placebo for Crohn's Disease

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Etanercept**		**Risk with Placebo**	**Risk difference with Etanercept**

Etanercept compared to Placebo for Crohn's Disease

Bibliography: Etanercept compared to Placebo for Crohn's Disease

Quality assessment							Summary of findings				
Clinical Response at 4 weeks (Primary Study Endpoint)											
43 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	9/20 (45.0%)	9/23 (39.1%)	**RR 0.87** (0.43 to 1.76)	450 per 1,000	59 fewer per 1,000 (257 fewer to 342 more)
Clinical Response at 2 weeks											
43 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/20 (25.0%)	11/23 (47.8%)	**RR 1.91** (0.80 to 4.57)	250 per 1,000	227 more per 1,000 (50 fewer to 893 more)
Clinical Response at 8 weeks											
43 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	6/20 (30.0%)	7/23 (30.4%)	**RR 1.01** (0.41 to 2.52)	300 per 1,000	3 more per 1,000 (177 fewer to 456 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Indirect comparison to placebo

b. C.I. crosses no effect line

References

1. Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, et al.. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. Aliment Pharmacol Ther. 2014 Jun;39(12):1349-62.
2. Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, et al. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2014 Apr;39(7):660-71.

3. Sandborn WJ, Hanauer SB, Katz S, Safdi M, Wolf DG, Baerg RD, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2001 Nov;121(5):1088-94.

PICO 59. In adult patients with active PsA and IBD despite treatment with an OSM, what are the benefits and harms of switching to TNFi (MABs) vs. switching to IL17i?

Summary: The literature searches did not identify any studies that addressed this PICO question. However, IL17i was not approved for IBD based on evidence from an RCT of harms in this patient population (the trial was discontinued early due to excess harms and lack of efficacy in the secukinumab arm).[1] This resulted in a warning on the IL17i package insert regarding harms in this population.

Quality of evidence across all critical outcomes: Moderate

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Hueber, 2012	RCT	6 weeks, with follow-up of secondary endpoints to 10 weeks	59 patients with moderate to severe Crohn's disease	Secukinumab (2X10 mg/kg intravenous, 39 patients) vs. placebo (20 patients)	Primary endpoint was change in Crohn's Disease Activity Index (CDAI) at 6 weeks. The difference between groups was not significant (change in CDAI score 33.9, 95% Bayesian credible interval -4.9 to 72.9), and area under the curve analysis at 4 to 10 weeks showed a significant difference (mean change in CDAI=49; 95% CI (2 to 96), p=0.043) favoring placebo. Adverse events were more common in the secukinumab group (74% vs. 50%) and the infection rate was much higher in the secukinumab group (43% vs. 0%).

References

1. Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PDR, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind, placebo-controlled trial. Gut 2012;61:1693–1700.

PICO 60. In adult patients with active PsA and IBD despite treatment with an OSM, what are the benefits and harms of switching to IL12/23i vs. switching to IL17i?

Summary: The literature searches did not identify any studies that addressed this PICO question. However, IL12/23i is approved for IBD and IL17i was not approved for IBD based on evidence of harms in this patient population (see PICO 59). This resulted in a warning on the IL17i package insert regarding harms in this population.

Quality of evidence across all critical outcomes: Moderate

References

1. Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PDR, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind, placebo-controlled trial. Gut 2012;61:1693–1700.

PICO 61. In adult patients with active PsA and IBD despite treatment with an OSM, what are the benefits and harms of switching to TNFi (MABs) vs. switching to IL12/23i?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 62. In adult patients with active PsA and IBD who are both OSM and biologic treatment-naïve, what are the benefits and harms of starting OSMs vs. starting TNFi (MABs)?

Summary. This PICO was addressed indirectly by one systematic review that included 3 RCTs. The studies looked at patients with acute ulcerative colitis naïve to OSM or biologics comparing treatment with infliximab vs. cyclosporine [1]. The only relevant outcome reported was serious adverse events, which showed no significant difference between treatment groups. However, the findings are inconclusive due to imprecision in the effect estimate.

Quality of evidence across all critical outcomes: Very low

Infliximab compared to Cyclosporine for PsA and IBD patients who are OSM and Biologic-naive **Bibliography: PICO 62 - PsA and IBD patients who are OSM and Biologic naive: OSM vs. TNFi.**	
Quality assessment	**Summary of findings**

Infliximab compared to Cyclosporine for PsA and IBD patients who are OSM and Biologic-naive

Bibliography: PICO 62 - PsA and IBD patients who are OSM and Biologic naive: OSM vs. TNFi.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With CYC	**With IFX**		**Risk with CYC**	**Risk difference with IFX**
Serious Adverse Events											
415 (1 systematic review with 3 RCTs)	serious [a]	not serious	very serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	14/206 (6.8%)	20/209 (9.6%)	**RR 1.41** (0.73 to 2.71)	68 per 1,000 (0.068)	**28 more per 1,000 (0.028)** (18 fewer to 116 more)

CI: Confidence interval; **CYC**: Cyclosporine; **IFX**: Infliximab; **RR:** Risk ratio

a. No mention in the review of randomization, allocation concealment, or blinding

b. Entire patient population are those with acute UC

c. Wide CI that crosses no effect line

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Narula N, Marshall JK, Colombel JF, Leontiadis GI, Williams JG, Muqtadir Z, et al. Systematic Review and Meta-Analysis: Infliximab or Cyclosporine as Rescue Therapy in Patients With Severe Ulcerative Colitis Refractory to Steroids. Am J Gastroenterol. 2016;111(4):477-491.

PICO 63. In adult patients with active PsA and diabetes who are both OSM and biologic treatment-naïve, what are the benefits and harms of starting OSM vs. starting TNFi?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. Two case series studies evaluated effects of diabetes on liver in patients with psoriasis on MTX treatment. One study [1] compared the impact of diabetes cumulatively with other risk factors such as obesity, alcohol consumption, chronic hepatitis B and C, while another study [2] studied impact of diabetes separately from other risk factors. Results show that diabetes has more impact on developing liver pathologies, such as fibrosis, in patients taking MTX at least 1000mg of cumulative dose.

Quality of evidence across all critical outcomes: Very low

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Rosenberg, 2007	Case series	Between 1975 and 2003	169 Patients with psoriasis and with/without diabetes mellitus type 2	Median cumulative dose MTX 1500-2100 mg	26 patients had one or more of the risk factors (diabetes mellitus type 2, overweight, alcohol over-consumption, and chronic hepatitis B or C) and 25 (96%) of these (median cumulative dose methotrexate 1500 mg) developed liver fibrosis. Of those without risk factor, 26 (58%) (p = 0.012) developed fibrosis (median cumulative dose methotrexate 2100 mg). Ten (38%) of the patients with risk factor(s) had severe fibrosis (stage 3–4) (mean cumulative dose methotrexate 1600 mg), while four (9%) (p = 0.0012) of those without risk factors had severe fibrosis (median cumulative dose methotrexate 1900 mg). Seven (100%) of the patients with diabetes mellitus developed liver fibrosis compared to 37 (52%) of those without. Four (57%) of the seven patients with diabetes developed severe fibrosis compared to nine (14%) of those without (p = 0.003)
Malatjalian, 1996	Case series	Mean treatment duration 3.38 yrs	104 patients with psoriasis and diabetes	MTX cumulative dose 1000 to 1500 mg	Progression of liver pathology to higher grade in patients with diabetes Odds Ratio 2.07 (0.35-12.35) p=0.42. Progression of liver pathology to grades IIIB and IV Odds Ratio 5.68 (1.34-24.39), p= 0.02

References:

1. Rosenberg P et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. Journal of Hepatology 46 (2007) 1111–1118
2. Malatjalian D et al. Methotrexate hepatotoxicity in psoriatics: Report of 104 patients from Nova Scotia, with analysis of risks from obesity, diabetes and alcohol consumption during long term follow-up. Can J Gastroenterol 1996;10(6):369-375.

PICO 64. In adult patients with active PsA and frequent serious infections who are both OSM and biologic treatment-naïve, what are the benefits and harms of starting OSMs vs. starting TNFi?

Summary: The literature searches did not identify any studies that addressed this PICO question. However, evidence concerning serious infections appears in the evidence base of earlier questions. Although the serious infection rate in most RCTs was so low that the findings were always imprecise, there is a black box warning against the use of TNFi in patients with recurrent serious infections.

Quality of evidence across all critical outcomes: Moderate

PICO 65. In adult patients with active PsA and frequent serious infections despite treatment with an OSM, what are the benefits and harms of switching to TNFi vs. switching to IL12/23i?

Summary: The literature searches did not identify any studies that directly addressed this PICO question. However, evidence concerning serious infections appears in the evidence base of earlier questions. The serious infection rate in most RCTs was so low that the findings were always imprecise. However, there is indirect evidence from a large retrospective cohort study (Yun et al. 2016) using Medicare data from RA patients.[1] The final cohort had 31,801 new courses of biologic therapy. The study compared hospitalized infection rates associated with the following biologic therapies: adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, and abatacept. Since abatacept had the lowest crude incidence rate of hospitalized infection (13.1/100 patients-years) it was used as the reference comparison. Biologic therapies with significantly higher adjusted hazard ratios (HR) for hospitalized infection compared to abatacept include etanercept (adjusted HR 1.24, 95% CI 1.07-1.45), infliximab (adjusted HR 1.39, 95% CI 1.21-1.60), and rituximab (adjusted HR 1.36, 95% CI 1.21-1.53).[1]

Quality of evidence across all critical outcomes: Very low

References:

1. Yun H et al. Comparative risk of hospitalized infection associated with biologic agents in rheumatoid arthritis patients enrolled in Medicare. Arth Rheumatol 2016; 68:56-66.

PICO 66. In adult patients with active PsA and frequent serious infections despite treatment with an OSM, what are the benefits and harms of switching to TNFi vs. switching to IL17i?

Summary: The literature searches did not identify any studies that addressed this PICO question. However, evidence concerning serious infections appears in the evidence base of earlier questions. However, the serious infection rate in most RCTs was so low that the findings were always imprecise.

Quality of evidence across all critical outcomes: Very low

Update: Additional PICO Questions

PICO 67. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to a TNFi compared to switching to abatacept?

Summary: Eleven placebo controlled RCTs (14 publications) indirectly addressed this PICO question. Nine studies (12 publications) compared TNFi versus placebo in PsA patients.[1-12] Two studies compared abatacept with placebo in PsA patients.[13,14] Statistically significant differences favoring TNFi over placebo were reported for all efficacy outcomes (ACR20, HAQ-DI, PASI-75, data not shown), while abatacept showed a significant benefit over placebo only for ACR20 (data not shown). No statistically significant differences with placebo occurred for any adverse events (see Table 2 for serious infections).

The adjusted indirect comparison method was used to calculate RRs for abatacept versus TNFi. The two TNFi studies (one using adalimumab, one using certolizumab) that reported infection rates had effect sizes in different directions, so these were separately compared to the abatacept trials. TNFi showed a significant benefit over abatacept for ACR20 and PASI-75, but not for HAQ-DI or rate of infection due to imprecision in effect estimates (Table 1).

Quality of evidence across all critical outcomes: Low

Table 1. TNFi compared to abatacept for patients with active PsA despite OSM
Bibliography: PICO 67: TNFi compared to abatacept for patients with active PsA despite OSM

Quality assessment							Summary of findings		
№ of participants	Risk of	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of		Relative effect	Anticipated absolute effects

Table 1. TNFi compared to abatacept for patients with active PsA despite OSM

Bibliography: PICO 67: TNFi compared to abatacept for patients with active PsA despite OSM

Quality assessment							Summary of findings				
(studies) Follow-up	**bias**					**evidence**	**With TNFi**	**With ABT**	**(95% CI)**	**Risk with TNFi**	**Risk difference with ABT**
ACR20, 12-24 weeks, Bucher adjusted indirect comparison											
2075 (11 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	TNFi	ABT	**RR 0.46** (0.30 to 0.69) **Favors TNFi**	583 per 1,000 (0.583)	**315 fewer per 1,000 (0.315)**(408 fewer to 181 fewer)
HAQ-DI[c], 12-24 weeks, Bucher adjusted indirect comparison											
1715 (9 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	TNFi	ABT	**RR 0.85** (0.43 to 1.66)	547 per 1,000 (0.547)	**82 fewer per 1,000 (0.082)**(312 fewer to 361 more)
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
1342 (10 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	TNFi	ABT	**RR 0.19** (0.08 to 0.43) **Favors TNFi**	494 per 1,000 (0.494)	**400 fewer per 1,000 (0.4)**(454 fewer to 282 fewer)
Infection, 12-24 weeks, Bucher adjusted indirect comparison											

Table 1. TNFi compared to abatacept for patients with active PsA despite OSM

Bibliography: PICO 67: TNFi compared to abatacept for patients with active PsA despite OSM

Quality assessment							Summary of findings				
524 (2 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	ADA	ABT	**RR 1.67** (0.75 to 3.69)	176 per 1,000 (0.176)	**118 more per 1,000 (0.118)**(44 fewer to 473 more)
698 (2 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	CZP	ABT	**RR 0.79** (0.52 to 1.21)	435 per 1,000 (0.435)	**91 fewer per 1,000 (0.091)**(209 fewer to 91 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

Table 2. TNFi or abatacept compared to placebo for PICO 67: Adverse events

Bibliography: PICO 67: TNFi versus abatacept for PsA patients who failed OSM.

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With ABT or TNFi	**With placebo**		**Risk with ABT or TNFi**	**Risk difference with placebo**
Serious infection – Abatacept vs. placebo											

Table 2. TNFi or abatacept compared to placebo for PICO 67: Adverse events

Bibliography: PICO 67: TNFi versus abatacept for PsA patients who failed OSM.

Quality assessment							Summary of findings				
506 (2 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	2/253 (0.8%)	0/253 (0%)	**RR 0.33** (0.03 to 3.13)	8 per 1,000 (0.008)	**5 fewer per 1,000 (0.005)** (0 fewer to 25 more)
Serious infection – TNFi vs. placebo											
1151 (5 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	4/587 (0.7%)	8/564 (1.4%)	**RR 1.85** (0.56 to 5.88)	7 per 1,000 (0.007)	**6 more per 1,000 (0.006)** (3 fewer to 34 more)

CI: Confidence interval; **RR:** Risk ratio

a. Comparison to placebo
b. Wide 95% CI

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73(1):48-55.
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PICO 68. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to an IL12/23i compared to switching to abatacept?

Summary: Five placebo-controlled RCTs indirectly addressed this PICO question. Three studies compared IL 12/23 (ustekinumab) with placebo in PsA patients.[1-3] Two studies compared abatacept with placebo in PsA patients.[4,5] Statistically significant differences favoring ustekinumab over placebo were reported for all efficacy outcomes (ACR20, HAQ-DI, PASI-75, data not shown), while abatacept showed a significant benefit over placebo only for ACR20 (data not shown). No statistically significant differences with placebo occurred for any adverse events (see Table 2 for serious infections).

The adjusted indirect comparison method was used to calculate RRs for abatacept versus ustekinumab. Ustekinumab showed a significant benefit over abatacept for PASI-75, but not for ACR20, HAQ-DI and rate of infections (there was imprecision in the effect estimates for these outcomes, see Table 1)).

Quality of evidence across all critical outcomes: Low

Table 1. IL12/23i compared to abatacept for patients with active PsA despite OSM
Bibliography: PICO 68: IL12/23i compared to abatacept for patients with active PsA despite OSM

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With IL12/23i	With ABT	Relative effect (95% CI)	Anticipated absolute effects: Risk with IL12/23i	Anticipated absolute effects: Risk difference with ABT
ACR20, 12-24 weeks, Bucher adjusted indirect comparison											
1579 (5 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	ABT	**RR 0.87** (0.61 to 1.24)	449 per 1,000 (0.449)	**58 fewer per 1,000** (175 fewer to 108 more)
HAQ-DI[c], 12-24 weeks, Bucher adjusted indirect comparison											

Table 1. IL12/23i compared to abatacept for patients with active PsA despite OSM

Bibliography: PICO 68: IL12/23i compared to abatacept for patients with active PsA despite OSM

Quality assessment							Summary of findings				
1370 (5 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	ABT	**RR 0.84** (0.43 to 1.65)	441 per 1,000 (0.441)	**71 fewer per 1,000** (251 fewer to 287 more)
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
1135 (5 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL12/23i	ABT	**RR 0.26** (0.14 to 0.49) **Favors IL12/23i**	569 per 1,000 (0.569)	**421 fewer per 1,000** (290 fewer to 489 fewer)
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
1349 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	ABT	**RR 0.94** (0.63 to 1.41)	211 per 1,000 (0.211)	**13 fewer per 1,000** (78 fewer to 87 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

Table 2. IL12/23i or abatacept compared to placebo for PICO 67: Adverse events

Bibliography: PICO 68: IL 12/23i versus abatacept for PsA patients who failed OSM.

Quality assessment	Summary of findings

Table 2. IL12/23i or abatacept compared to placebo for PICO 67: Adverse events

Bibliography: PICO 68: IL 12/23i versus abatacept for PsA patients who failed OSM.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With ABT or IL12/23i	**With placebo**		**Risk with ABT or IL12/23i**	**Risk difference with placebo**
Serious infection – Abatacept vs. placebo											
506 (2 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	2/253 (0.8%)	0/253 (0%)	**RR 0.33** (0.03 to 3.13)	8 per 1,000	**5 fewer per 1,000** (0 fewer to 25 more)
Serious infection – Ustekinumab vs. placebo											
925 (2 RCTs)	not serious	serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	4/616 (0.6%)	2/309 (0.6%)	**RR 1.19** (0.29 to 4.98)	6 per 1,000 (0.006)	**1 more per 1,000** (4 fewer to 24 more)

CI: Confidence interval; **RR:** Risk ratio

a. Comparison to placebo
b. Wide 95% CI

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382(9894):780-789.
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3. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73(6):990-999.
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5. Mease PJ, Gottlieb AB, van der Heijde D, FitzGerald O, Johnsen A, Nys M, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. Ann Rheum Dis. 2017.

PICO 69. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to an IL17i compared to switching to abatacept?

Summary: Nine placebo-controlled RCTs indirectly addressed this PICO question. Seven studies compared IL17i to placebo: One study compared ixekizumab to placebo,[1] three studies compared secukinumab to placebo,[2-4] and three studies compared brodalumab to placebo[5-7] (note: brodalumab is currently FDA-approved for psoriasis but not PsA). Two studies compared abatacept with placebo in PsA patients.[8,9] Statistically significant differences favoring IL17i over placebo were reported for all efficacy outcomes (ACR20, HAQ-DI, PASI-75, data not shown), while abatacept showed a significant benefit over placebo only for ACR20 (data not shown). No statistically significant differences with placebo occurred for any adverse events (see Table 2 for serious infections).

The adjusted indirect comparison method was used to calculate RRs for abatacept versus IL17i. IL17i showed a significant benefit over abatacept for PASI-75, but not for ACR20, HAQ-DI and rate of infections (there was imprecision in the effect estimates for these outcomes).

Quality of evidence across all critical outcomes: Low

Table 1. IL17i compared to abatacept for patients with active PsA despite OSM
Bibliography: PICO 69: IL17i compared to abatacept for patients with active PsA despite OSM

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With IL17i	With ABT	Relative effect (95% CI)	Anticipated absolute effects: Risk with IL17i	Anticipated absolute effects: Risk difference with ABT
ACR20, 12-24 weeks, Bucher adjusted indirect comparison											
1463 (7 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	ABT	**RR 0.76** (0.53 to 1.09)	505 per 1,000 (0.505)	**121 fewer per 1,000** (0.121)(237 fewer to 45 more)
HAQ-DI[c], 12-24 weeks, Bucher adjusted indirect comparison											

Table 1. IL17i compared to abatacept for patients with active PsA despite OSM

Bibliography: PICO 69: IL17i compared to abatacept for patients with active PsA despite OSM

Quality assessment							Summary of findings				
1151 (6 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	ABT	**OR 0.98** (0.39 to 2.50)	556 per 1,000 (0.556)	5 fewer per 1,000 (0.005) (228 fewer to 202 more)[d]
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
1167 (9 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL17i	ABT	**RR 0.21** (0.10 to 0.42) **Favors IL17i**	643 per 1,000 (0.643)	**508 fewer per 1,000** (0.508)(373 fewer to 579 fewer)
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
1026 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	ABT	**RR 0.74** (0.46 to 1.20)	321 per 1,000 (0.321)	**83 fewer per 1,000** (0.083)(173 fewer to 64 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).
d. Absolute risk differences calculated from odds ratios obtained using the Bucher method.

Table 2. IL17i or abatacept compared to placebo for PICO 69: Adverse events

Bibliography: PICO 69: IL 17i versus abatacept for PsA patients who failed OSM.

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With ABT or IL17i	**With placebo**		**Risk with ABT or IL17i**	**Risk difference with placebo**
Serious infection – Abatacept vs. placebo											
506 (2 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	2/253 (0.8%)	0/253 (0%)	**RR 0.33** (0.03 to 3.13)	8 per 1,000 (0.008)	**5 fewer per 1,000 (0.005)** (8 fewer to 25 more)
Serious infection – IL17i vs. placebo											
1189 (3 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	18/685 (2.6%)	5/406 (1.2%)	**RR 0.56** (0.23 to 1.33)	26 per 1,000 (0.026)	**11 fewer per 1,000 (0.011)** (20 fewer to 9 more)

CI: Confidence interval; **RR:** Risk ratio

a. Comparison to placebo
b. Wide 95% CI

Working Group quality of evidence categories:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017;76(1):79-87.
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9. Mease PJ, Gottlieb AB, van der Heijde D, FitzGerald O, Johnsen A, Nys M, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. Ann Rheum Dis. 2017.

PICO 70. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to a second TNFi compared to switching to abatacept?

Summary: This PICO question was addressed indirectly by three double-blind RCTs (4 publications). In addition to lack of direct drug comparisons, only 19% to 39% of patients in each study had prior TNFi exposure. One study (2 publications) involving PsA patients compared TNFi (CZP) to placebo.[1,2] Two studies compared abatacept with placebo in PsA patients.[3,4] CZP showed statistically significant benefit over placebo for all effectiveness outcomes (ACR20, HAQ-DI, and PASI-75, data not shown), while abatacept showed significant benefit over placebo only for ACR20 (data not shown). For serious infections there were no significant between-group differences, but with very high imprecision due to the low number of events (data not shown).

The adjusted indirect comparison method was used to calculate RRs for CZP vs. abatacept. For ACR20 we also performed this calculation using data only from patients with prior TNFi exposure (two studies reported separate data for these patients). CZP showed a significant benefit over abatacept for PASI75, but not for other outcomes (all were imprecise, see Table 1).

Quality of evidence across all critical outcomes: Low

Table 1. TNFi compared to abatacept for patients with active PsA despite TNFi
Bibliography: PICO 70: TNFi compared to abatacept for patients with active PsA despite TNFi

Quality assessment							Summary of findings				
									Relative effect (95% CI)	Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With TNFi	With ABT		Risk with TNFi	Risk difference with ABT
ACR20, 12-24 weeks, Bucher adjusted indirect comparison											
780 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	CZP	ABT	**RR 0.69** (0.45 to 1.06)	638 per 1,000 (0.638)	**198 fewer per 1,000 (0.198)**(351 fewer to 38 more)
ACR20, 12-24 weeks, Bucher adjusted indirect comparison, TNFi-exposed											

Table 1. TNFi compared to abatacept for patients with active PsA despite TNFi

Bibliography: PICO 70: TNFi compared to abatacept for patients with active PsA despite TNFi

Quality assessment							Summary of findings				
339 (2 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	CZP	ABT	**RR 0.32** (0.10 to 1.01)	593 per 1,000 (0.593)	**403 fewer per 1,000 (0.403)**(534 fewer to 6 more)
HAQ-DI[c], 12-24 weeks, Bucher adjusted indirect comparison											
578 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	CZP	ABT	**RR 1.14** (0.59 to 2.21)	580 per 1,000 (0.580)	**16 more per 1,000 (0.016)** (213 fewer to 210 more)[d]
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
512 (3 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	CZP	ABT	**RR 0.41** (0.19 to 0.90) **Favors CZP**	622 per 1,000 (0.622)	367 fewer per 1,000 (0.367)
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
698 (2 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	CZP	ABT	**RR 0.79** (0.52 to 1.21)	435 per 1,000 (0.435)	**91 fewer per 1,000 (0.091)**(209 fewer to 91 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).
d. Absolute risk differences calculated from odds ratios obtained using the Bucher method.

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73(1):48-55.
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3. Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum. 2011;63(4):939-948.
4. Mease PJ, Gottlieb AB, van der Heijde D, FitzGerald O, Johnsen A, Nys M, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. Ann Rheum Dis. 2017.

PICO 71. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to an IL12/23i compared to switching to abatacept?

Summary: This PICO question was addressed indirectly by four double-blind RCTs. In addition to lack of direct drug comparisons, only 28% to 50% of patients in each study had prior TNFi exposure. Two studies involving PsA patients compared IL12/23i (ustekinumab) to placebo.[1,2] Two studies compared abatacept with placebo in PsA patients.[3,4] Ustekinumab showed statistically significant benefit over placebo for all effectiveness outcomes (ACR20, HAQ-DI, and PASI-75, data not shown), while abatacept showed significant benefit over placebo only for ACR20 (data not shown). For serious infections there were no significant between-group differences, but with very high imprecision due to the low number of events (data not shown).

The adjusted indirect comparison method was used to calculate RRs for IL12/23i vs. abatacept. For ACR20 we also performed this calculation using data only from patients with prior TNFi exposure (two studies reported separate data for these patients). Ustekinumab showed a significant benefit over abatacept for PASI75, but not for other outcomes (all were imprecise, see Table 1).

Quality of evidence across all critical outcomes: Low

Table 1. IL12/23i compared to abatacept for patients with active PsA despite TNFi
Bibliography: PICO 71: IL12/23i compared to abatacept for patients with active PsA despite TNFi

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							With IL12/23i	With ABT		Risk with IL12/23i	Risk difference with ABT
ACR20, 12-24 weeks, Bucher adjusted indirect comparison											
964 (4 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	ABT	**RR 0.79** (0.50 to 1.22)	433 per 1,000 (0.433)	**91 fewer per 1,000 (0.091)**(216 fewer to 95 more)
ACR20, 12-24 weeks, Bucher adjusted indirect comparison, TNFi-exposed patients											

Table 1. IL12/23i compared to abatacept for patients with active PsA despite TNFi

Bibliography: PICO 71: IL12/23i compared to abatacept for patients with active PsA despite TNFi

Quality assessment							Summary of findings				
394 (2 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	ABT	**RR 0.67** (0.31 to 1.42)	356 per 1,000 (0.356)	**117 fewer per 1,000 (0.117)**(246 fewer to 150 more)
HAQ-DI[c], 12-24 weeks, Bucher adjusted indirect comparison											
755 (4 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	ABT	**RR 0.72** (0.36 to 1.47)	389 per 1,000 (0.389)	**109 fewer per 1,000 (0.109)**(249 fewer to 183 more)
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
695 (4 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL12/23i	ABT	**RR 0.16** (0.06 to 0.42) **Favors IL12/23i**	531 per 1,000 (0.531)	**446 fewer per 1,000 (0.446)**(499 fewer to 308 fewer)
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
735 (2 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	ABT	**RR 0.80** (0.48 to 1.33)	271 per 1,000 (0.271)	**54 fewer per 1,000** (141 fewer to 89 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI

c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

1. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73(6):990-999.
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3. Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum. 2011;63(4):939-948.
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PICO 72. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to an IL17i compared to switching to abatacept?

Summary: This PICO was addressed indirectly by seven double-blind RCTs. In addition to lack of direct drug comparisons, only 29% to 50% of patients in each study had prior TNFi exposure. Two studies involving PsA patients compared Brodalumab to placebo.[1,2] Three studies compared Secukinumab to Placebo in patients with PsA.[3-5] One study compared Ixekizumab to placebo in patients with PsA.[6] Two studies compared abatacept with placebo in PsA patients.[7, 8] IL17i showed statistically significant benefit over placebo for all effectiveness outcomes (ACR20, HAQ-DI, and PASI-75, data not shown), while abatacept showed significant benefit over placebo only for ACR20 (data not shown). For serious infections there were no significant between-group differences, but with very high imprecision due to the low number of events (data not shown).

The adjusted indirect comparison method was used to calculate RRs for IL17i vs. abatacept. For ACR20 we also performed this calculation using data only from patients with prior TNFi exposure (two studies reported separate data for these patients). IL17i showed significant benefit over abatacept for PASI-75 and ACR20, but the additional analysis of ACR20 using only patients with prior TNFi exposure did not show a significant difference between drugs (there was imprecision due to a wide 95% CI). The findings for HAQ-DI and infections were inconclusive due to imprecision in effect estimates.

Quality of evidence across all critical outcomes: Low

Table 1. IL17i compared to abatacept for patients with active PsA despite TNFi
Bibliography: PICO 72: IL17i compared to abatacept for patients with active PsA despite TNFi

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							With IL17i	With ABT		Risk with IL17i	Risk difference with ABT
ACR20, 12-24 weeks, Bucher adjusted indirect comparison											

Table 1. IL17i compared to abatacept for patients with active PsA despite TNFi

Bibliography: PICO 72: IL17i compared to abatacept for patients with active PsA despite TNFi

Quality assessment							Summary of findings				
1254 (6 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL17i	ABT	**RR 0.66** (0.46 to 0.97) **Favors IL17i**	479 per 1,000 (0.479)	**163 fewer per 1,000 (0.163)**(259 fewer to 15 fewer)
ACR20, 12-24 weeks, Bucher adjusted indirect comparison, TNFi-exposed											
293 (2 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	ABT	**RR 0.73** (0.37 to 1.43)	354 per 1,000 (0.354)	**96 fewer per 1,000 (0.096)**(223 fewer to 152 more)
HAQ-DI[c], 12-24 weeks, Bucher adjusted indirect comparison											
942 (5 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	ABT	**RR 1.20** (0.64 to 2.25)	545 per 1,000 (0.545)	**36 more per 1,000 (0.036)**(175 fewer to 367 more)[d]
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
865 (6 RCTs)	Not serious	Not serious	Serious[a]	Not serious	None	⨁⨁⨁◯ MODERATE	IL17i	ABT	**RR 0.21** (0.07 to 0.60) **Favors IL17i**	594 per 1,000 (0.594)	**469 fewer per 1,000 (0.469)**(552 fewer to 238 fewer)

Table 1. IL17i compared to abatacept for patients with active PsA despite TNFi

Bibliography: PICO 72: IL17i compared to abatacept for patients with active PsA despite TNFi

Quality assessment							Summary of findings				
Infection, 12-24 weeks, Bucher adjusted indirect comparison											
1026 (3 RCTs)	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	ABT	**RR 0.74** (0.46 to 1.20)	321 per 1,000 (0.321)	**83 fewer per 1,000** (0.083)(173 fewer to 64 more)

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. HAQ-DI measured as proportion of patients who achieved minimum clinically important improvement (>0.3 or 0.35 in different studies).
d. Absolute risk differences calculated from odds ratios obtained using the Bucher method.

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

References:

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PICO 73. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to a TNFi compared to switching to tofacitinib?

Summary: Ten placebo controlled RCTs (13 publications) indirectly addressed this PICO question. Nine studies (12 publications) compared TNFi versus placebo in PsA patients.[1-12] One study that pooled data from two psoriasis RCTs compared tofacitinib (5 mg twice daily) to placebo in a subgroup of patients with PsA.[13] The only relevant outcome presented in this study was PASI-75, so this is the only outcome that was compared between TNFi and tofacitinib. Statistically significant differences favored TNFi over placebo and tofacitinib over placebo for this outcome (data not shown). An adjusted indirect comparison found no significant difference in PASI-75 between TNFi and tofacitinib, but the finding was imprecise due to a wide CI that overlapped with the line of no effect (Table 1).

A search update in March 2018 identified two new RCTs comparing tofacitinib to placebo in patients with PsA.[14,15] The guideline panel had previously reviewed these studies in abstract form when formulating recommendations. Only one of the trials (Mease et al.[14]) enrolled a population of patients with prior OSM treatment but no prior TNFi exposure. This study also had a comparison arm of patients receiving adalimumab. At 3 months, tofacitinib showed significant benefit over placebo for ACR 20, HAQ-DI, and PASI 75, and no significant difference between tofacitinib and adalimumab for these outcomes. The tofacitinib versus placebo comparison is moderate quality due to indirectness, and the tofacitinib versus adalimumab comparison is moderate quality due to imprecision. These trials do not change the imprecision in the adjusted indirect comparisons and do not alter the overall quality of evidence.

Quality of evidence across all critical outcomes: Low

Table 1. TNFi compared to tofacitinib for patients with active PsA despite OSM
Bibliography: PICO 73: TNFi compared to tofacitinib for patients with active PsA despite OSM

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							With TNFi	With TOF		Risk with TNFi	Risk difference with TOF
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											

Table 1. TNFi compared to tofacitinib for patients with active PsA despite OSM

Bibliography: PICO 73: TNFi compared to tofacitinib for patients with active PsA despite OSM

Quality assessment							Summary of findings				
10 RCTs	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	TNFi	TOF	**RR 0.90** (0.28 to 2.92)	494 per 1,000 (0.494)	**113 fewer per 1,000 (0.113)**(352 fewer to 199 more)[c]

CI: Confidence interval; **RR:** Risk ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. Absolute risk differences calculated from odds ratios obtained using the Bucher method.

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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15. Gladman D, Rigby W, Azevedo VF, Behrens F, Blanco R, Kaszuba A, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. NEJM. 2017;377(16):1525-1536.

PICO 74. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to an IL12/23i compared to switching to tofacitinib?

Summary: Four placebo-controlled RCTs indirectly addressed this PICO question. Three studies compared IL 12/23 (ustekinumab) with placebo in PsA patients.[1-3] One study that pooled data from two psoriasis RCTs compared tofacitinib (5 mg twice daily) to placebo in a subgroup of patients with PsA.[4] The only relevant outcome presented in this study was PASI-75, so this is the only outcome that was compared between ustekinumab and tofacitinib. Statistically significant differences favored ustekinumab over placebo and tofacitinib over placebo for this outcome (data not shown). An adjusted indirect comparison found no significant difference in PASI-75 between IL12/23i and tofacitinib, but the finding was imprecise due to a wide CI that overlapped with the line of no effect (Table 1).

A search update in March 2018 identified two new RCTs comparing tofacitinib to placebo in patients with PsA.[5,6] The guideline panel had previously reviewed these studies in abstract form when formulating recommendations. Only one of the trials (Mease et al.[5]) enrolled a population of patients with prior OSM treatment but no prior TNFi exposure. Tofacitinib showed significant benefit over placebo for ACR 20, HAQ-DI, and PASI 75. The tofacitinib versus placebo comparison is moderate quality due to indirectness. These trials do not change the imprecision in the adjusted indirect comparisons and do not alter the overall quality of evidence.

Quality of evidence across all critical outcomes: Low

Table 1. IL12/23i compared to tofacitinib for patients with active PsA despite OSM
Bibliography: PICO 74: IL12/23i compared to tofacitinib for patients with active PsA despite OSM

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**			**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With IL12/23i	**With TOF**		**Risk with IL12/23i**	**Risk difference with TOF**
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											
4 RCTs	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL12/23i	TOF	**OR 0.84** (0.27 to 2.65)	569 per 1,000	**43 fewer per 1,000 (0.043)**(306 fewer to 209 more)[c]

CI: Confidence interval; **OR:** Odds ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. Absolute risk differences calculated from odds ratios obtained using the Bucher method.

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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PICO 75. In adult patients with active PsA despite treatment with an OSM, what are the benefits and harms of switching to an IL17i compared to switching to tofacitinib?

Summary: Nine placebo-controlled RCTs indirectly addressed this PICO question. Seven studies compared IL17i to placebo: One study compared ixekizumab to placebo,[1] three studies compared secukinumab to placebo,[2-4] and three studies compared brodalumab to placebo[5-7] (note: brodalumab is currently FDA-approved for psoriasis but not PsA). One study that pooled data from two psoriasis RCTs compared tofacitinib (5 mg twice daily) to placebo in a subgroup of patients with PsA.[8] The only relevant outcome presented in this study was PASI-75, so this is the only outcome that was compared between IL17i and tofacitinib. Statistically significant differences favored IL17i over placebo and tofacitinib over placebo for this outcome (data not shown). An adjusted indirect comparison found no significant difference in PASI-75 between IL17i and tofacitinib, but the finding was imprecise due to a wide CI that overlapped with the line of no effect (Table 1).

A search update in March 2018 identified two new RCTs comparing tofacitinib to placebo in patients with PsA.[9,10] The guideline panel had previously reviewed these studies in abstract form when formulating recommendations. Only one of the trials (Mease et al.[9]) enrolled a population of patients with prior OSM treatment but no prior TNFi exposure. Tofacitinib showed significant benefit over placebo for ACR 20, HAQ-DI, and PASI 75. The tofacitinib versus placebo comparison is moderate quality due to indirectness. These trials do not change the imprecision in the adjusted indirect comparisons and do not alter the overall quality of evidence.

Quality of evidence across all critical outcomes: Low

Table 1. IL17i compared to tofacitinib for patients with active PsA despite OSM
Bibliography: PICO 75: IL17i compared to tofacitinib for patients with active PsA despite OSM

Quality assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence			Relative effect (95% CI)	Anticipated absolute effects	
							With IL17i	With TOF		Risk with IL17i	Risk difference with TOF
PASI 75, 12-24 weeks, Bucher adjusted indirect comparison											

Table 1. IL17i compared to tofacitinib for patients with active PsA despite OSM

Bibliography: PICO 75: IL17i compared to tofacitinib for patients with active PsA despite OSM

Quality assessment							Summary of findings				
9 RCTs	Not serious	Not serious	Serious[a]	Serious[b]	None	⨁⨁◯◯ LOW	IL17i	TOF	**OR 0.52** (0.15 to 1.85)	643 per 1,000 (0.643)	**159 fewer per 1,000 (0.159)**(430 fewer to 126 more)[c]

CI: Confidence interval; **OR:** Odds ratio

a. Indirect comparison, all studies compared drug to placebo, only 50-75% of patients had prior OSM exposure.
b. Wide 95% CI
c. Absolute risk differences calculated from odds ratios obtained using the Bucher method.

Working Group quality of evidence categories:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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1. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017;76(1):79-87.
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PICO 76. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to a second TNFi compared to switching to tofacitinib?

Summary: See summary for PICO 73. The available tofacitinib study did not separately report data for patients with prior TNFi exposure, and did not report the percentage of patients with PsA who had prior TNFi exposure (the percentage with prior biologic exposure was 26% for the overall population of patients with psoriasis), so the comparison in PICO 73 can be used as indirect evidence. In the main population of patients with psoriasis the findings did not differ for biologic-naïve and biologic-exposed patients.

A search update in March 2018 identified two new RCTs comparing tofacitinib to placebo in patients with PsA.[1,2] The guideline panel had previously reviewed these studies in abstract form when formulating recommendations. Only one of the trials (Gladman et al.[2]) enrolled a population of patients with prior TNFi exposure. At 3 months, tofacitinib showed significant benefit over placebo for ACR 20 and HAQ-DI; only the 10 mg dose showed significant benefit over placebo for PASI 75. This new evidence is moderate quality due to indirectness, does not change the imprecision in the adjusted indirect comparisons and therefore does not alter the overall quality of evidence.

Quality of evidence across all critical outcomes: Low

References:

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PICO 77. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to an IL12/23i compared to switching to tofacitinib?

Summary: See summary for PICO 74, with explanation in PICO 76.

Quality of evidence across all critical outcomes: Low

PICO 78. In adult patients with active PsA despite treatment with a TNFi monotherapy, what are the benefits and harms of switching to an IL17i compared to switching to tofacitinib?

Summary: : See summary for PICO 75, with explanation in PICO 76.

Quality of evidence across all critical outcomes: Low

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