Supplementary Appendix to Lillegraven S, Paulshus Sundlisæter N, Aga A-B, et al. Effect of tapered vs stable treatment with tumor necrosis factor inhibitors on disease flares in patients with rheumatoid arthritis in remission: a randomized, open label, non-inferiority trial

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eAppendix 1. Inclusion and exclusion criteria

Inclusion criteria

1. Rheumatoid arthritis (RA) according to the 2010 ACR/EULAR classification criteria
2. Male or non-pregnant, non-nursing female
3. >18 years of age and <80 years of age
4. Any disease duration
5. Sustained remission for ≥12 months according to DAS or DAS28, with documented remission status at a minimum of 2 consecutive visits during the last 18 months.
6. DAS <1.6 and no swollen joints at inclusion.
7. Unchanged treatment with TNFi and synthetic DMARD co-medication during the previous 12 months, with a stable or reduced dose of glucocorticosteroids
8. Subject capable of understanding and signing an informed consent form
9. Provision of written informed consent

Exclusion criteria

1. Abnormal renal function, defined as serum creatinine >142 μmol/L in female and >168 μmol/L in male, or a glomerular filtration rate <40 mL/min/1.73 m^2.
2. Abnormal liver function (defined as ASAT/ALAT >3x upper normal limit), active or recent hepatitis, cirrhosis.
3. Major co-morbidities, such as severe malignancies, severe diabetic mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (New York Heart Association classification 3 or 4) and/or severe respiratory diseases.
4. Leukopenia and/or thrombocytopenia.
5. Inadequate birth control, pregnancy, and/or breastfeeding
6. Indications of active TB.
7. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol impossible.

Abbreviations:
ACR: American College of Rheumatology. ALAT: Alanine transaminase. ASAT: Aspartate transaminase. DAS: Disease Activity Score. DAS28: Disease Activity Score based on 28 joint count. DMARD: Disease-modifying antirheumatic drugs. EULAR: European League Against Rheumatism.

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eAppendix 2. End of study inclusion

Our study was designed to include 160 patients, however due to a slower than expected inclusion, the study recruitment was stopped at 99 patients. This decision was based solely on elapsed inclusion time, and not on a preliminary analysis of the data. Expanding the trial to a multi-national effort was discussed, but decided against. The effect of this smaller than planned sample size is reduced power to conclude the non-inferiority of tapering to stable treatment, assuming this is in fact the case. While our study does not conclude non-inferiority, this is not due to a lack of power, instead a statistically significant difference was observed between the two treatment groups. This conclusion is drawn with the predetermined Type 1 error of 5%.

At the time of designing this trial, we wanted to include a subpopulation of well-controlled RA patients in whom we believed tapering to withdrawal would be a feasible strategy. However, Norway is a small country, and remission without clinical signs of inflammation on TNFi turned out to be a less common state than we expected. With increasing adherence to updated treatment recommendations and availability of TNFi over the years, we think that the defined patient population is more relevant today as the goal of sustained remission has become more achievable.

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eFigure 1. Disease activity during flare.

Analyzed in those who flared in the primary analysis population, defined as all randomized patients meeting the study entry criteria, and with no protocol deviations affecting the treatment efficacy (defined as failure to follow the treatment regimen or withdrawal from the study). Panel A: C-reactive protein (mg/dL) at the visit before a flare occurred, at the flare visit and the visit after a flare occurred. Panel B: 44 swollen joint count at the visit before a flare occurred, at the flare visit and the visit after a flare occurred. Boxes mark first and third quartiles, the band inside the box is the second quartile (the median), while the whiskers indicate the highest and lowest values within 1.5 x the interquartile range. Dots denote individual patients (outliers).
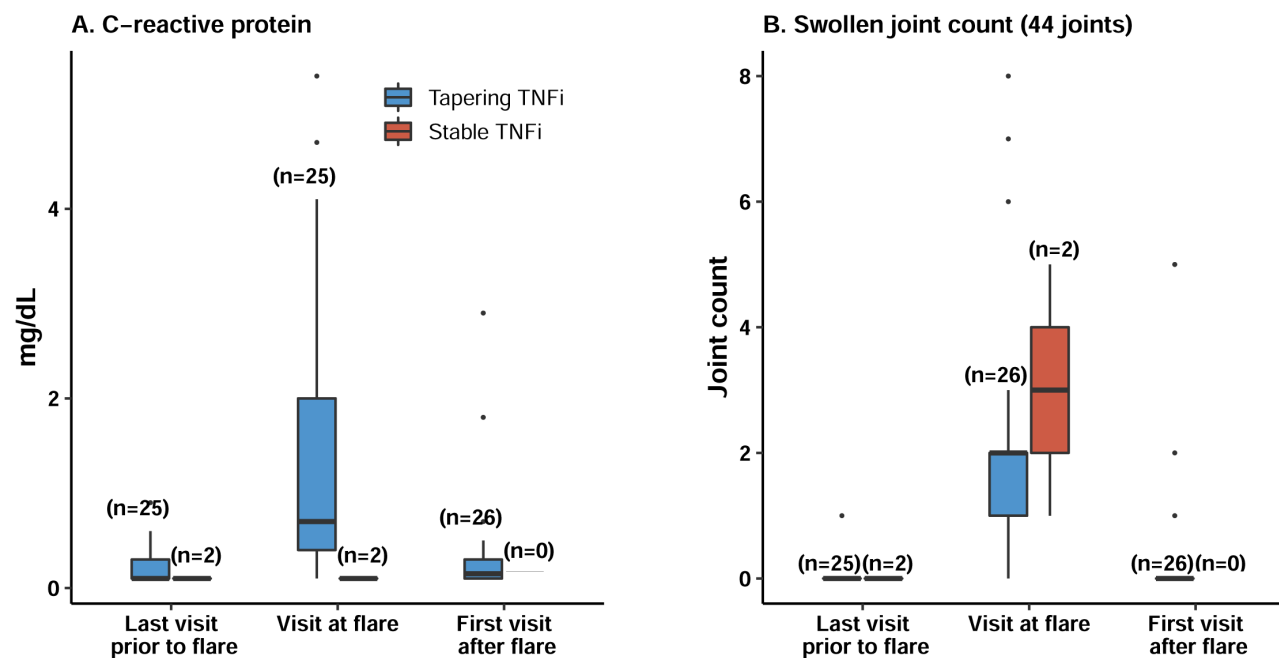
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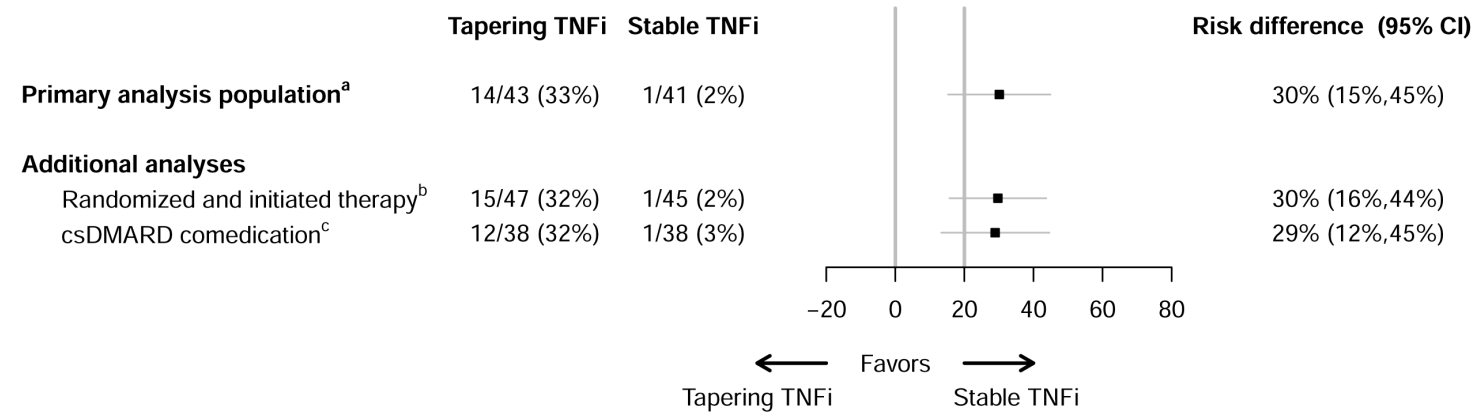
eFigure 2. Analyses with flare according to the definition based on Disease Activity Score (DAS) and swollen joint count.

	Tapering TNFi	Stable TNFi		Risk difference (95% CI)
Primary analysis population[a]	14/43 (33%)	1/41 (2%)		30% (15%,45%)
Additional analyses				
Randomized and initiated therapy[b]	15/47 (32%)	1/45 (2%)		30% (16%,44%)
csDMARD comedication[c]	12/38 (32%)	1/38 (3%)		29% (12%,45%)

Favors ← Tapering TNFi   Stable TNFi →

Flare was defined as a combination of disease activity score (DAS) above the cut-off for remission (1.6), a change in DAS of at least 0.6, and at least two swollen joints.
The dotted, vertical line represents the noninferiority margin. csDMARD indicates conventional synthetic disease-modifying antirheumatic drug.

[a] The analysis was performed in all randomized patients meeting the study entry criteria, and with no protocol deviations affecting the treatment efficacy (defined as failure to follow the treatment regimen or withdrawal from the study).
[b] Four patients who were randomized but did not have verified initiation of treatment are excluded, two from each group.
[c] Analysis performed in patients within the primary analysis population who used csDMARD comedication.

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eTable 1. Trial enrollment by study site.

	Site	University function	Community/ regional hospital[a]	Number of patients enrolled
1	Diakonhjemmet Hospital	x	x	50
2	Drammen Hospital		x	11
3	Haukeland University Hospital	x	x	10
4	Ålesund Hospital		x	10
5	Østfold Hospital		x	7
6	University Hospital of North Norway	x	x	5
7	Revmatismesykehuset Lillehammer		x	4
8	Helgelandssykehuset Mo i Rana		x	1
9	Martina Hansens Hospital		x	1

[a]The large majority of patients with rheumatoid arthritis in Norway receive treatment and follow-up at rheumatology departments in hospitals.

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eTable 2. Secondary outcomes

Continuous variables[a]	Tapering TNFi	Stable TNFi	Tapering TNFi	Stable TNFi	Difference at 12 months (95% CI)[b]
	Baseline		Change 0-12 months		
Measures of disease activity					
Disease Activity Score[c], mean (SD)	0.8 (0.3)	0.9 (0.4)	0.2 (0.5)	0.1 (0.4)	0.1 (-0.0,0.3)
Disease Activity Score[c], AUC	-	-	1.0 (0.4)	0.9 (0.4)	0.1 (-0.1,0.3)
Disease Activity Score in 28 joints[d], mean (SD)	1.5 (0.5)	1.7 (0.6)	0.4 (0.7)	0.1 (0.7)	0.3 (0.1,0.6)
Disease Activity Score in 28 joints[d], AUC	-	-	1.9 (0.6)	1.7 (0.6)	0.2 (-0.1,0.5)
Simplified Disease Activity Index[e], median (IQR)	0.8 (0.4,1.5)	0.7 (0.3,3.1)	1.7 (3.6)	0.7 (2.9)	0.8 (-0.6,2.2)
Simplified Disease Activity Index[e], AUC	-	-	2.7 (2.5)	2.0 (2.1)	0.8 (-0.6,2.1)
Clinical Disease Activity Index[f], median (IQR)	0.4 (0.2,1.2)	0.3 (0.1,3.0)	1.5 (3.4)	0.8 (2.9)	0.4 (-0.9,1.8)
Clinical Disease Activity Index[f], AUC	-	-	2.4 (2.5)	1.8 (2.1)	0.7 (-0.7,2.0)
Swollen-joint count[g], mean (SD)	0.0 (0.0)	0.0 (0.0)	0.2 (0.8)	0.2 (0.8)	0.0 (-0.4,0.5)
Tender-joint count (Ritchie Articular Index)[h], median (IQR)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.5 (1.6)	0.1 (0.9)	0.2 (-0.3,0.6)
Erythrocyte sedimentation rate, mm/hr[i], median (IQR)	7.0 (5.0,13.0)	8.0 (5.0,15.0)	4.9 (9.9)	-1.5 (8.7)	5.6 (2.6,8.6)
C-reactive protein, mg/dL, normal value <0.4 mg/dL[j], median (IQR)	0.1 (0.1,0.3)	0.1 (0.1,0.2)	0.2 (0.7)	-0.1 (0.5)	0.3 (0.1,0.5)
Patient's global assessment[k], median (IQR)	3.0 (1.0,9.0)	2.0 (1.0,12.0)	4.1 (13.4)	4.2 (14.7)	-1.8 (-7.5,3.8)
Physician's global assessment[k], median (IQR)	0.0 (0.0,2.0)	0.0 (0.0,2.0)	2.5 (7.7)	1.0 (5.9)	0.7 (-1.8,3.2)
Functional outcomes					
PROMIS Physical Function[l], mean (SD)	53.4 (6.7)	52.9 (8.4)	-0.5 (5.6)	-0.9 (5.4)	0.6 (-1.6,2.7)
EuroQol-5 Dimensions[m], median (IQR)	0.8 (0.8,1.0)	1.0 (0.8,1.0)	0.0 (0.1)	-0.1 (0.2)	0.1 (0.0,0.1)
Fatigue visual-analogue scale[n], median (IQR)	7.0 (1.0,22.0)	3.0 (0.0,24.0)	3.4 (19.9)	5.2 (18.9)	-1.7 (-10.1,6.6)
Joint pain visual-analogue scale[n], median (IQR)	4.0 (1.0,9.0)	2.0 (1.0,11.0)	3.2 (16.1)	4.8 (11.9)	-2.0 (-8.0,4.0)
SF-36 Physical Functioning[o], median (IQR)	90.0 (80.0,100.0)	90.0 (80.0,100.0)	-4.3 (14.2)	-0.7 (10.5)	-3.5 (-8.8,1.8)
SF-36 Bodily Pain[o], median (IQR)	90.0 (70.0,100.0)	90.0 (77.5,100.0)	-2.0 (18.1)	-8.4 (20.6)	6.0 (-2.0,14.0)
SF-36 Role-physical[o], median (IQR)	100.0 (100.0,100.0)	100.0 (75.0,100.0)	-16.9 (31.2)	-1.5 (33.3)	-13.4 (-27.5,0.7)
SF-36 Role-emotional[o], median (IQR)	100.0 (100.0,100.0)	100.0 (100.0,100.0)	-5.0 (24.5)	-3.3 (24.5)	-2.4 (-12.8,8.0)

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eTable 2. Secondary outcomes

	Tapering TNFi	Stable TNFi	Tapering TNFi	Stable TNFi	
SF-36 Mental health[o], median (IQR)	88.0 (76.0,92.0)	88.0 (84.0,96.0)	2.1 (11.2)	0.1 (10.0)	0.6 (-3.3,4.5)
SF-36 Social Functioning[o], median (IQR)	100.0 (87.5,100.0)	100.0 (87.5,100.0)	-1.5 (17.7)	-1.8 (12.0)	0.0 (-5.7,5.7)
SF-36 Vitality[o], median (IQR)	70.0 (60.0,80.0)	70.0 (50.0,80.0)	-3.0 (18.5)	-2.4 (14.2)	0.1 (-6.7,6.9)
SF-36 General Health[o], median (IQR)	85.0 (70.0,90.0)	80.0 (70.0,95.0)	-4.5 (17.1)	-7.5 (15.4)	3.1 (-3.7,9.9)
SF-36 Physical Component Summary Score[o], median (IQR)	54.0 (50.7,58.1)	54.5 (46.5, 57.9)	-3.2 (6.5)	-2.4 (7.4)	-0.7 (-3.9,2.5)
SF-36 Mental Component Summary Score[o], median (IQR)	55.9 (51.1,58.0)	56.8 (55.0,58.4)	0.3 (6.8)	-0.4 (6.5)	0.7 (-2.2,3.5)
RAID[p]	0.9 (0.3,1.7)	0.5 (0.0,2.0)	0.3 (1.2)	0.3 (1.3)	-0.0 (-0.5,0.4)
Radiographic joint damage					
Total van der Heijde modified Sharp score[q], median (IQR)	6.5 (1.5,12.5)	5.0 (1.5,13.0)	0.3 (1.2)	0.1 (0.6)	0.2 (-0.2,0.6)
van der Heijde Sharp Erosion, median (IQR)	2.0 (1.0,4.5)	2.0 (0.5,4.5)	0.1 (0.5)	0.0 (0.5)	0.0 (-0.2,0.3)
van der Heijde Sharp Joint Space Narrowing, median (IQR)	2.5 (0.5,7.0)	1.0 (0.0,8.0)	0.2 (0.8)	0.0 (0.3)	0.2 (-0.1,0.4)
Ultrasound outcomes[r]					
Total power Doppler signal score, median (IQR)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.2 (1.0)	0.0 (1.1)	0.1 (-0.2,0.5)
Total grey scale score, median (IQR)	1.0 (0.0,3.0)	1.0 (0.0,3.0)	-0.3 (4.0)	-1.0 (5.5)	-0.1 (-1.1,1.0)
Medication					
Total triamcinolone hexacetonide dose (mg), no	NA	NA	363	94	
Total number of intraarticular injections, no	NA	NA	21	5	

Categorized variables[a]	Baseline		Change 0-12 months		Difference at 12 months (95% CI)[b]
Measures of disease activity					
Disease Activity Score remission[c], no (%)	43 (100%)	41 (100%)	37 (88%)	34 (85%)	4% (-14%, 22%)
Disease Activity Score in 28 joints remission[d], no (%)	43 (100%)	37 (90%)	33 (79%)	32 (80%)	-1% (-20%,17%)
Simplified Disease Activity Index remission[e], no (%)	42 (98%)	31 (76%)	31 (74%)	26 (68%)	7% (-14%, 28%)
Clinical Disease Activity Index remission[f], no (%)	41 (95%)	30 (73%)	33 (79%)	26 (65%)	13% (-7%, 34%)
ACR/EULAR remission[s], no (%)	36 (84%)	27 (66%)	28 (67%)	24 (63%)	6% (-15%, 28%)
No swollen joints, no (%)	43 (100%)	41 (100%)	36 (86%)	36 (90%)	-5% (-20%,10%)
No tender joints, no (%)	41 (95%)	36 (88%)	36 (86%)	33 (83%)	3% (-15%, 21%)

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eTable 2. Secondary outcomes

	Tapering TNFi	Stable TNFi	Tapering TNFi	Stable TNFi	
Imaging outcomes					
No radiographic progression 0-12 months, progression defined as vdHSS ≥ 1.0 units/year, no (%)	NA	NA	34 (81%)	36 (90%)	-9% (-24%, 6%)
No radiographic progression 0-12 months, progression defined as vdHSS ≥ 0.5 units/year, no (%)	NA	NA	30 (70%)	30 (73%)	-4% (-23%,16%)
No radiographic progression 0-12 months, progression defined as vdHSS ≥ SDC, 1.38 units/year, no (%)	NA	NA	40 (95%)	38 (95%)	-
No radiographic progression 0-12 months, progression defined as vdHSS ≥ 2.0 units/year, no (%)	NA	NA	41 (98%)	40 (100%)	-
No radiographic progression 0-12 months, progression defined as vdHSS ≥ 5.0 units/year, no (%)	NA	NA	41 (98%)	40 (100%)	-
No power Doppler signal in any joint, no (%)	40 (93%)	38 (95%)	35 (85%)	35 (90%)	-4% (-19%,10%)
Medication					
TNFi monotherapy, no (%)	5 (12%)	3 (7%)	5 (12%)	3 (7%)	-
TNFi in combination with csDMARD, no (%)	38 (88%)	38 (93%)	20 (48%)	38 (93%)	-
Etanercept, no (%)	19 (44%)	18 (44%)	14 (33%)	18 (44%)	-
Infliximab, no (%)	9 (21%)	0 (0%)	5 (12%)	0 (0%)	-
Adalimumab, no (%)	2 (5%)	4 (10%)	1 (2%)	4 (10%)	-
Golimumab, no (%)	1 (2%)	4 (10%)	0 (0%)	4 (10%)	-
Certolizumab pegol, no (%)	12 (28%)	15 (37%)	5 (12%)	15 (37%)	-
csDMARD comedication					-
Methotrexate, no (%)	36 (84%)	35 (85%)	33 (79%)	35 (85%)	-
Salazopyrine, no (%)	1 (2%)	1 (2%)	1 (2%)	1 (3%)	-
Leflunomide, no (%)	1 (2%)	2 (5%)	1 (2%)	2 (5%)	-
Patients with any intraarticular glucocorticoid injections 0-12 months, no (%)	NA	NA	13 (30%)	4 (10%)	21% (4%, 37%)
Any prednisolone use over 12 months, no (%)	NA	NA	5 (12%)	0 (0%)	-

Abbrevations: ACR: American College of Rheumatology, AUC: Area under the curve. csDMARD: conventional synthetic disease-modifying antirheumatic drugs. EQ-5D: EuroQol-5 Dimensions. EULAR: European Alliance of Associations for Rheumatology. IQR: Interquartile range. P.O: Per os. PROMIS: Patient-reported Outcomes Measurement Information Score. RAID: Rheumatoid Arthritis Index of Disease. SD: Standard deviation. SF-36: 36-item Short Form Health Survey. vdHSS: van der Heijde modified Sharp score.

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[a] Analyzed in the primary analysis population, defined as all randomized patients meeting the study entry criteria, and with no protocol deviations affecting the treatment efficacy (defined as failure to follow the treatment regimen or withdrawal from the study).

[b] Mean difference at 12 months in patients with visit 4 data, values in tapered group – values in stable group. Adjusted for baseline.

[c] The Disease Activity Score for 44-joint counts (DAS) ranges from 0 to 10, with higher scores indicating more disease activity, remission defined as a DAS value <1.6 [1].

[d] The Disease Activity Score for 28-joint counts with Erythrocyte sedimentation rate (DAS28 ESR) ranges from 0 to 10 with higher scores indicating more disease activity, remission defined as a DAS28 value <2.6 [2].

[e] The Simplified Disease Activity Index (SDAI) ranges from 0 to 86, with higher scores indicating more disease activity, remission defined as a SDAI value $\leq$3.3 [3,4].

[f] The Clinical Disease Activity Index (CDAI) ranges from 0 to 76, with higher scores indicating more disease activity, CDAI remission defined as a CDAI value $\leq$2.8 [4,5].

[g] The swollen-joint count is the number of swollen joints out of 44 joints assessed.

[h] The tender joint count is performed by the Ritchie articular index [6] assessing tenderness of 26 joint regions, the index ranges from 0 to 3 for individual measures and the sum 0 to 78 overall, with higher scores indicating more tenderness.

[i] At time of baseline visit, normal values might be subject to laboratory.

[j] At time of baseline visit, normal values might be subject to laboratory. To convert C-reactive protein to mg/L (SI unit), multiply by 10

[k] The patient's and physician's global assessments are self-reported and physician-reported, respectively, overall assessments of disease with use of a visual analogue scale that ranges from 0 to 100 mm, with higher scores indicating more severe disease.

[l] Patient-reported Outcomes Measurement Information Score (PROMIS) [7] 20-item short form range from 0 to 100, with scores lower than 50 indicating disability worse than average.

[m] EuroQol-5 Dimensions (EQ-5D) [8,9], UK weighted; Range from 1 (best possible health), through 0 (death) to -0.59 (worse than death).

[n] Fatigue and joint pain is self-reported with use of a visual analogue scale that ranges from 0 to 100 mm, with higher scores indicating more severe fatigue.

[o] The 36-item Short Form Health Survey (SF-36) ranges from 0 to 100 [10].

[p] The Rheumatoid Arthritis Index of Disease (RAID) is calculated based on seven numerical rating scales (NRS) questions. Each NRS is assessed as a number between 0 and 10. The seven NRS correspond to pain, function, fatigue, sleep, emotional wellbeing, physical wellbeing and coping/self-efficacy.

[q] Total van der Heijde modified Sharp score [11] is a score of erosions and joint space narrowing based on radiographs of hands and feet, with range from 0 to 448 (with higher scores indicating greater joint damage), and quantifies erosions on a scale from 0 to 280 and joint-space narrowing on a scale from 0 to 168.

[r] Ultrasound examination was performed using 0-3 semi quantitative scoring systems [12] for both grey-scale and power Doppler in each of the following 32 joints; metacarpophalangeal joints (MCP) 1-5, radiocarpal joint, intercarpal joint, distal radioulnar joint, elbow, knee, talocrural joint and metatarsophalangeal joints (MTP) 1-5 bilaterally. Ranges from 0 to 192 for total ultrasound score, and from 0 to 96 for grey-scale and power Doppler ultrasound score.

[s] ACR/EULAR Boolean remission [13] is defined as tender joint count ≤1, swollen-joint count ≤1, C-reactive protein ≤1mg/dL and patient's global assessment ≤10.

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eTable 3. Flares according to type of tumor necrosis factor inhibitor.

	Tapering TNFi N=43	Stable TNFi N=41
Etanercept, no (%)	14/19 (74%)	1/18 (6%)
Certolizumab pegol, no (%)	6/12 (50%)	0/15 (0%)
Golimumab, no (%)	1/1 (100%)	0/4 (0%)
Adalimumab, no (%)	1/2 (50%)	1/4 (25%)
Infliximab, no (%)	5/9 (56%)	0/0 (-)

eTable 4. Response to reinstated treatment after flare

Characteristic[a]	Tapering TNFi	Stable TNFi
ACR20 response[b], no (%)	10/23 (43%)	0/0
ACR50 response[b], no (%)	9/23 (39%)	0/0
ACR70 response[b], no (%)	9/23 (39%)	0/0
ACR90 response[b], no (%)	5/23 (22%)	0/0
EULAR response: Good/Moderate[c], no (%)	16/24 (67%)	0/0
EULAR response: None[c], no (%)	8/24 (33%)	0/0
Disease Activity Score remission, no (%)	23/26 (88%)	0/0
FDA major clinical response[d], no (%)	5/19 (26%)	0/0

Abbreviations: ACR: American College of Rheumatology. EULAR: European Alliance of Rheumatology Associations. FDA: The U.S. Food and Drug Administration.

[a] Time to first clinical examination after a flare varied from few weeks to four months depending on the timing of the protocolized next visit.
[b] Improvement of 20%/50%/70%/90% (respectively for ACR20/50/70/90) in the number of tender and number of swollen joints, in combination with a 20%/50%/70%/90% (respectively for ACR20/50/70/90) improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure, visual analog joint pain scale, and erythrocyte sedimentation rate or C-reactive protein.
[c] A good EULAR response is a decrease in Disease Activity Score (DAS) by more than 1.2 points and resulting in a DAS of 2.4 or less. A moderate EULAR response is a decrease in DAS of more than 0.6 points and resulting in a DAS of 3.7 or less.
[d] The U.S. Food and Drug Administration major clinical response requires achieving ACR70 response at the current visit and at each visit within the previous 6 months. Results for patients with sufficient data post-flare.

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