**SUPPLEMENTARY APPENDIX 6: Evidence Report**

# 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis


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*PICO-specific instructions for the Voting Panel appear in italics below each PICO.*

**Citations in this document appear as**:
AuthorLastName year [Citation#] where
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# Notes

**GRADE Working Group grades of evidence definitions**

Very low quality: We are very uncertain about the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

**Abbreviations**

Adverse Event = a medication "side-effect"
Acute Phase Reactant = blood test for inflammation
AS = ankylosing spondylitis
ASDAS = Ankylosing Spondylitis Disease Activity Score
ASQOL = Ankylosing Spondylitis Quality of Life instrument
axSpA = axial spondyloarthritis
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index
BASFI = Bath Ankylosing Spondylitis Functional Index
BASMI = Bath Ankylosing Spondylitis Metrology Index (a composite measure of range of motion for the central skeleton)
CI's = confidence intervals
CRP = c-reactive protein (blood test for inflammation)
DFI = Dougados Functional Index
ESSG = European Spondyloarthropathy Study Group criteria (Dougados 1991)[1]
FACIT-F Functional Assessment of Chronic Illness Therapy-Fatigue
FEV = forces expiratory volume; a test of lung function
F/U = follow up
GI = gastrointestinal
GL = guidelines
IBD = inflammatory bowel disease
HHS = Harris Hip Score (assesses functional status, pain, and ROM related to hip in order to assess surgical outcomes)
MD = mean difference (the absolute difference between intervention and control groups or between baseline and final values for a measurement, such as the BASDAI or BASFI)
mNY = modified New York Classification Criteria for ankylosing spondylitis (van der Linden 1984)[2]
nr-AxSpA – non-radiographic axial spondyloarthritis
NR = not reported
PICO = Patient/Intervention/Comparison/Outcome formatted question used in the GRADE system
PsA = psoriatic arthritis
pts = patients
SD's = standard deviations
RCT = randomized controlled trial

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## PICO 1: In adults with active or stable AS, is continuous treatment with NSAIDs more effective than on-demand treatment with NSAIDs in improving outcomes?

*Guidance to voters: If your vote is different for active and stable disease, vote only for active disease and we will adjust the PICO next time. Please note this in your comments.*

Summary: This PICO was directly addressed by 2 RCTs. The first was included in the 2015 axSpA GL: a 2-year open-label (patients unblinded) study (Wanders 2005)[3]. All patients in this study began treatment with celecoxib (100 mg twice daily), but patients were permitted to increase this dosage to 200 mg twice daily or could switch to another NSAID while maintaining the same treatment strategy. There were no significant differences between groups in any patient reported outcomes, with wide confidence intervals, and high risk of bias. The change in mSASSS (read by a radiologist in a blinded manner) was lower in the continuous treatment group. Hypertension and depression were more common in the continuous treatment group.

Since 2015 guideline, an additional randomized multicenter trial (ENRADAS) (Sieper 2016)[4] was published comparing on-demand treatment to continuous treatment with diclofenac. Continuous treatment consisted of a maximum of 150 mg/day, with at least 50% of this recommended maximal dose taken daily. Switching to a different NSAID was permitted for intolerance or inefficacy, but TNFi treatment was prohibited. Change in mSASSS from baseline was numerically greater for the continuous group, but not significantly different from the on-demand group. Incidence of adverse events (inflammatory bowel disease, cardiovascular disorders, and overall significant adverse events) was not significantly different between groups.

When combining data from both RCTs for change in mSASSS from baseline (Table 1, below, 2nd outcome), this outcome was downgraded for inconsistency in findings between the two studies, and it is possible that this was due to a difference in the medications used.

Overall quality of evidence across all critical outcomes: Low to Moderate

## Table 1: Continuous versus on-demand treatment with NSAIDs for patients with active AS

| Table 1: Continuous versus on-demand treatment with NSAIDs for patients with active AS<br>Bibliography: Wanders 2005[3]; Sieper 2016[4] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Certainty assessment** | | | | | | | **Summary of findings** | | | | |
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall certainty of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| | | | | | | | **With on-demand NSAID** | **With Continuous NSAID** | | **Risk with on-demand NSAID** | **Risk difference with Continuous NSAID** |
| mSASSS change from base (ITT), 2 yrs | | | | | | | | | | | |
| 167 (1 RCT) (Sieper) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 82 | 85 | - | - | MD **0.58 higher** (0.28 lower to 1.44 higher) |
| mSASSS change from base (patients with all radiographs), 2 yrs | | | | | | | | | | | |
| 272 (2 RCTs) (Wanders & Sieper) | not serious | serious [c] | not serious | serious [d] | none | ⊕⊕◯◯ LOW | 134 | 138 | - | - | MD **0.32 lower** (1.88 lower to 1.24 higher) |
| SAE: Cardiovascular disorders, 2 yrs | | | | | | | | | | | |
| 122 (1 RCT) (Sieper) | not serious | not serious | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 2/60 (3.3%) | 3/62 (4.8%) | **OR 1.47** (0.24 to 9.15) | 33 per 1,000 | **15 more per 1,000** (25 fewer to 207 more) |
| SAE: IBD (colitis or Crohn's), 2 years | | | | | | | | | | | |
| 122 (1 RCT) (Sieper) | not serious | not serious | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 3/60 (5.0%) | 1/62 (1.6%) | **OR 0.31** (0.03 to 3.08) | 50 per 1,000 | **34 fewer per 1,000** (48 fewer to 89 more) |
| SAEs (total), 2 yrs | | | | | | | | | | | |
| 122 (1 RCT) (Sieper) | not serious | not serious | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 21/60 (35.0%) | 19/62 (30.6%) | **OR 0.82** (0.38 to 1.75) | 350 per 1,000 | **44 fewer per 1,000** (180 fewer to 135 more) |
| BASDAI | | | | | | | | | | | |
| 150 (1 RCT) (Wanders) | serious [e] | not serious | not serious | serious [f] | none | ⊕⊕◯◯ LOW | 74 | 76 | - | - | MD **6 lower** (11.95 lower to 0.05 lower) |
| Pain | | | | | | | | | | | |
| 150 (1 RCT) (Wanders) | serious [e] | not serious | not serious | serious [b] | none | ⊕⊕◯◯ LOW | 74 | 76 | - | - | MD **6 lower** (12.59 lower to 0.59 higher) |
| Fatigue | | | | | | | | | | | |
| 150 (1 RCT) (Wanders) | serious [e] | not serious | not serious | serious [b] | none | ⊕⊕◯◯ LOW | 74 | 76 | - | - | MD **5 lower** (11.76 lower to 1.76 higher) |
| Stiff | | | | | | | | | | | |
| 150 (1 RCT) (Wanders) | serious [e] | not serious | not serious | serious [b] | none | ⊕⊕◯◯ LOW | 74 | 76 | - | - | MD **5 lower** (11.41 lower to 1.41 higher) |
| AcutePhaseReag | | | | | | | | | | | |
| 150 (1 RCT) (Wanders) | serious [e] | not serious | not serious | serious [b] | none | ⊕⊕◯◯ LOW | 74 | 76 | - | - | MD **3.7 lower** (8.37 lower to 0.97 higher) |
| BASFI | | | | | | | | | | | |
| 150 (1 RCT) (Wanders) | serious [e] | not serious | not serious | serious [b] | none | ⊕⊕◯◯ LOW | 74 | 76 | - | - | MD **3 lower** (9.76 lower to 3.76 higher) |
| ROM | | | | | | | | | | | |

| Table 1: Continuous versus on-demand treatment with NSAIDs for patients with active AS<br>Bibliography: Wanders 2005[3]; Sieper 2016[4] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With on-demand NSAID | With Continuous NSAID | | Risk with on-demand NSAID | Risk difference with Continuous NSAID |
| 150 (1 RCT) (Wanders) | serious [e] | not serious | not serious | serious [b] | none | ⊕⊕◯◯ LOW | 74 | 76 | - | - | MD **0.2 lower** (0.87 lower to 0.47 higher) |
| Hypertension | | | | | | | | | | | |
| 214 (1 RCT) (Wanders) | not serious | not serious | not serious | serious [g] | none | ⊕⊕⊕◯ MODERATE | 3/103 (2.9%) | 10/111 (9.0%) | **OR 3.30** (0.88 to 12.35) | 29 per 1,000 | **61 more per 1,000** (3 fewer to 241 more) |
| Dyspepsia | | | | | | | | | | | |
| 214 (1 RCT) (Wanders) | not serious | not serious | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 39/103 (37.9%) | 46/111 (41.4%) | **OR 1.16** (0.67 to 2.01) | 379 per 1,000 | **35 more per 1,000** (89 fewer to 172 more) |
| Depression | | | | | | | | | | | |
| 214 (1 RCT) (Wanders) | serious [e] | not serious | not serious | serious [f] | none | ⊕⊕◯◯ LOW | 4/103 (3.9%) | 15/111 (13.5%) | **OR 3.87** (1.24 to 12.07) | 39 per 1,000 | **96 more per 1,000** (9 more to 289 more) |

**CI:** Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

## Explanations

a. Not applicable; single study.
b. Single study; wide 95% CI crosses line of no difference.
c. 2 studies report differing findings for outcome measure.
d. Wide 95% CI spans line of no difference.
e. Unblinded study (patients).
f. Single study; wide 95% CI.
g. Single study; low incidence of event. Very wide 95% CI spans line of no difference.

### Table 2. Additional Evidence from RCTs (not incorporated above due to lack of SD's/CI's)

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 619, Sieper 2016[4] | RCT | 2 years | 167 patients with AS | Continuous vs. on-demand treatment with diclofenac | Both treatment groups showed significant mSASSS progression (Brunner test p=0.00011).<br>Mean BASDAI (corrected for baseline) values decreased within the completer population over 2 years of treatment: from 4.1 to 2.7 in the continuous group and from 4.2 to 3.2 in the on-demand group. |

## PICO 33: In adults with active or stable non-radiographic axial SpA, is continuous treatment with NSAIDs more effective than on-demand treatment with NSAIDs in improving outcomes?

*Guidance to voters: This is similar to PICO 1, which posed the same question in AS. If your vote is different for active and stable disease, vote only for active disease and we will adjust the PICO next time. Please note this in your comments.*

Summary: This PICO question was not directly addressed by any studies.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 5: In adults with active AS, are certain TNFi more effective than other TNFi in improving outcomes?

Summary: This PICO was directly addressed by 2 RCTs. The first was a small head-to-head comparison of infliximab and etanercept (Giardina 2009)[5]; the second was the same RCT published in three reports that compared the biosimilar CT-P13 versus the originator molecule infliximab (Tables 2 and 3; Park 2013; Park 2016; Park 2016)[6-8]. Numerous indirect comparisons can be made by utilizing the results of 20+ RCTs (TNFi vs. placebo) assessed in at least 9 recent systematic reviews/meta-analyses (Wang 2018; Shu 2015; Maxwell 2015; Corbett 2016; Chen 2016; Wu 2015; Sepriano 2017; Ungprasert 2017; Baji 2014)[9-17], in addition to the 4 meta-analyses previously reported in the 2015 guidelines (Migliore 2012; McLeod 2007; Machado 2013; Ren 2013)[18-21].

Direct comparisons: The 2-year open-label infliximab vs. etanercept RCT (Giardina 2009) enrolled 50 patients with active AS and was reported in the 2015 guidelines. No statistically significant between group differences were reported at 2 years for ASAS 20/40, BASDAI or BASFI, although patients showed significant improvements with infliximab at 12 weeks over baseline for these outcomes (see Table 1).

The second RCT contributing direct evidence to this PICO question consists of the PLANETAS trial, which compared the pharmacokinetics, efficacy, and safety of infliximab to the biosimilar CT-P13. Results of this randomized, double-blind, multicenter, parallel-group trial in patients with ankylosing spondylitis, are reported in separate publications of 30-week follow-up (see Table 2) and 54-week follow-up (Table 3). PLANETAS enrolled patients with active AS for >=3 months. The initial report only included median changes from baseline for BASDAI, BASFI, and BASMI scores (no measures of dispersion/statistical analyses), so more detailed measures of these outcomes were included for 54-weeks of follow up. Results from both of the PLANETAS studies indicate no significant differences between CT-P13 and infliximab for most major efficacy outcomes or adverse event rates, though low event rates coupled with a relatively small enrollment led to very high measurement imprecision.

Indirect comparisons: These are largely based on the data present from the studies in PICO 6 and compared indirectly through multiple prior systematic reviews/network meta-analyses. Though not formally reviewed as evidence for this PICO question, in general, these systematic reviews and network analyses did not identify differences in efficacy between the TNFi's. For example, a systematic review/meta-analysis (Ungprasert 2017)[16] found that the likelihood of achieving the ASAS20 response in patients with AS who failed or could not tolerate NSAIDs was not significantly different between older TNFi's or certolizumab pegol. Similarly, a meta-analysis (Baji 2014)[17] compared the efficacy and safety of infliximab-biosimilar with other biological drugs for the treatment of active AS. This study included 13 RCTs with over 2000 total patients and concluded that the infliximab biosimilar had similar efficacy and safety profile to that of other biologicals.

Some evidence indicated that infliximab was associated with lower rates of IBD flares (see PICO 32, below) than etanercept. According to one meta-analysis, monoclonal antibodies are associated with a higher rate of tuberculosis compared with etanercept Souto 2014[22]. Uveitis, as an outcome, is addressed in PICO 29, below.

Overall quality of evidence for all critical outcomes: Moderate

## Table 1: Head-to-head RCT comparison of infliximab and etanercept

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Infliximab | Control: Etanercept | Relative (95% CI) | Absolute | | |
| **Health Status: BASDAI (follow-up mean 104 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1,2] | none | 25 | 25 | - | mean 0 higher (unable to calculate CI)[1] | ⊕⊕⊕O MODERATE | CRITICAL |
| **Functional Status: BASFI (follow-up mean 104 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 25 | 25 | - | MD 0 higher (unable to calculate CI)[1] | ⊕⊕⊕O MODERATE | CRITICAL |

[1] no confidence intervals provided
[2] small sample size

## Table 2: CT-P13 compared to infliximab, 30wks

**Table 2: CT-P13 compared to infliximab for improving outcomes in active AS patients, 30wks**
**Bibliography: Park 2013[6]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With INX, 30 wks | With CT-P13 | | Risk with INX, 30 wks | Risk difference with CT-P13 |
| **ASAS 20 response, 30 wks** | | | | | | | | | | | |
| 250 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 84/125 (67.2%) | 79/125 (63.2%) | OR 0.84 (0.50 to 1.41) | 672 per 1,000 | **40 fewer per 1,000** (71 more to 166 fewer) |
| **ASAS 40, 30 wks** | | | | | | | | | | | |
| 250 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 55/125 (44.0%) | 58/125 (46.4%) | OR 1.10 (0.67 to 1.81) | 440 per 1,000 | **24 more per 1,000** (95 fewer to 147 more) |
| **ASDAS-CRP (mean change from base), 30 wks** | | | | | | | | | | | |
| 250 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 116 | 113 | - | - | MD **0.1 lower** (0.41 lower to 0.21 higher) |
| **Overall treatment-emergent AEs, 30 wks** | | | | | | | | | | | |
| 250 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 78/122 (63.9%) | 83/128 (64.8%) | OR 1.04 (0.62 to 1.75) | 639 per 1,000 | **9 more per 1,000** (116 fewer to 117 more) |
| **Urinary tract infection, 30 wks** | | | | | | | | | | | |
| 250 (1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⊕⊕⊕◯ MODERATE | 0/122 (0.0%) | 5/128 (3.9%) | OR 10.91 (0.60 to 199.46) | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| **Tonsilitis, 30 wks** | | | | | | | | | | | |
| 250 (1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⊕⊕⊕◯ MODERATE | 2/122 (1.6%) | 0/128 (0.0%) | OR 0.19 (0.01 to 3.95) | 16 per 1,000 | **13 fewer per 1,000** (16 fewer to 45 more) |
| **Tuberculosis, 30 wks** | | | | | | | | | | | |
| 250 (1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⊕⊕⊕◯ MODERATE | 1/122 (0.8%) | 2/128 (1.6%) | OR 1.92 (0.17 to 21.46) | 8 per 1,000 | **7 more per 1,000** (7 fewer to 142 more) |
| **Cardiac AEs, 30 wks** | | | | | | | | | | | |

| Table 2: CT-P13 compared to infliximab for improving outcomes in active AS patients, 30wks<br>Bibliography: Park 2013[6] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⊕⊕⊕◯<br>MODERATE | 1/122<br>(0.8%) | 1/128<br>(0.8%) | OR 0.95<br>(0.06 to 15.40) | 8 per 1,000 | **0 fewer per 1,000**<br>(8 fewer to 105 more) |
| **Appendicitis, 30 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⊕⊕⊕◯<br>MODERATE | 1/122<br>(0.8%) | 0/128<br>(0.0%) | OR 0.32<br>(0.01 to 7.81) | 8 per 1,000 | **6 fewer per 1,000**<br>(8 fewer to 52 more) |
| **Carcinoma, 30 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⊕⊕⊕◯<br>MODERATE | 0/122<br>(0.0%) | 1/128<br>(0.8%) | OR 2.88<br>(0.12 to 71.44) | 0 per 1,000 | **Not calculable** |

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

## Explanations

a. Not applicable; single study.
b. Single study; 95% CI includes possibility of no difference.
c. Single study; low event rate, extremely wide 95% CI including possibility of no difference.

## Table 3: CT-P13 compared to infliximab, 54wks

| Table 3: CT-P13 compared to INX, 54 weeks for improving outcomes in active AS patients<br>Bibliography: Park 2016[7]; Park 2016[8] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall certainty of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| | | | | | | | **With INX, 54 wks** | **With CT-P13** | | **Risk with INX, 54 wks** | **Risk difference with CT-P13** |
| **ASAS20** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 82/125<br>(65.6%) | 73/125<br>(58.4%) | OR 0.74<br>(0.44 to 1.23) | 656 per 1,000 | **71 fewer per 1,000**<br>(200 fewer to 45 more) |
| **ASAS40, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 56/125<br>(44.8%) | 59/125<br>(47.2%) | OR 1.10<br>(0.67 to 1.81) | 448 per 1,000 | **24 more per 1,000**<br>(96 fewer to 147 more) |
| **ASAS partial response, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 18/125<br>(14.4%) | 18/125<br>(14.4%) | OR 1.00<br>(0.49 to 2.03) | 144 per 1,000 | **0 fewer per 1,000**<br>(68 fewer to 111 more) |
| **BASDAI change, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 125 | 125 | - | - | MD **0.3 lower**<br>(0.86 lower to 0.26 higher) |
| **BASFI change, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 125 | 125 | - | - | MD **0.2 lower**<br>(0.75 lower to 0.35 higher) |
| **SF-36 physical comp, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 125 | 125 | - | - | MD **0.2 higher**<br>(1.98 lower to 2.38 higher) |
| **BASMI change, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 125 | 125 | - | - | MD **0.2 lower**<br>(0.58 lower to 0.18 higher) |
| **Chest expansion, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 125 | 125 | - | - | MD **0.2 lower**<br>(0.51 lower to 0.11 higher) |

| Table 3: CT-P13 compared to INX, 54 weeks for improving outcomes in active AS patients<br>Bibliography: Park 2016[7]; Park 2016[8] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| **Overall serious adverse events, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 8/122 (6.6%) | 10/128<br>(7.8%) | OR 1.21<br>(0.46 to 3.17) | 66 per 1,000 | **13 more per 1,000**<br>(34 fewer to 116 more) |
| **Overall treatment-related SAEs, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 5/122 (4.1%) | 4/128<br>(3.1%) | OR 0.75<br>(0.20 to 2.88) | 41 per 1,000 | **10 fewer per 1,000**<br>(33 fewer to 69 more) |
| **Active tuberculosis, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⊕⊕⊕◯<br>MODERATE | 1/122 (0.8%) | 2/128<br>(1.6%) | OR 1.92<br>(0.17 to 21.46) | 8 per 1,000 | **7 more per 1,000**<br>(7 fewer to 142 more) |
| **Malignancy, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⊕⊕⊕◯<br>MODERATE | 0/122 (0.0%) | 1/128<br>(0.8%) | OR 2.88<br>(0.12 to 71.44) | 0 per 1,000 | **0 fewer per 1,000**<br>(0 fewer to 0 fewer) |
| **Abnormal liver function test, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 15/122<br>(12.3%) | 16/128<br>(12.5%) | OR 1.02<br>(0.48 to 2.16) | 123 per 1,000 | **2 more per 1,000**<br>(60 fewer to 109 more) |
| **Upper respiratory tract infection, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 8/122 (6.6%) | 12/128<br>(9.4%) | OR 1.47<br>(0.58 to 3.74) | 66 per 1,000 | **28 more per 1,000**<br>(26 fewer to 142 more) |
| **Latent tuberculosis, 54 wks** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⊕⊕⊕◯<br>MODERATE | 6/122 (4.9%) | 9/128<br>(7.0%) | OR 1.46<br>(0.50 to 4.24) | 49 per 1,000 | **21 more per 1,000**<br>(24 fewer to 131 more) |
| **Treatment-associated SAEs and discontinuation** | | | | | | | | | | | |
| 250<br>(1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯<br>MODERATE | 9/122 (7.4%) | 11/128<br>(8.6%) | OR 1.18<br>(0.47 to 2.96) | 74 per 1,000 | **12 more per 1,000**<br>(38 fewer to 117 more) |

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

### Explanations

a. Not applicable; single study.
b. Single study; 95% CI includes possibility of no difference.
c. Single study; very low event incidence leading to extremely wide CI, including possibility of no difference.

## PICO 37: In adults with active non-radiographic axial SpA, are certain TNFi more effective than other TNFi in improving outcomes?

*Guidance to voters: This is similar to PICO 5, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any studies. For very indirect evidence, a network analysis (Corbett 2016)[12] in AS and nr-axSpA reported the nr-axSpA results based on data from of 5 RCTs (each comparing adalimumab, etanercept, infliximab, or certolizumab to placebo) and did not find any consistent differences (comparing BASDAI50, ASAS20, ASAS40, mean difference BASDAI change from baseline, BASMI, mean difference SF-36 PCS, and mean difference SF-36 MCS) between TNFi agents.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 6: In adults with active AS despite treatment with NSAIDs, are TNFi more effective than no treatment with TNFi in improving outcomes?

*Guidance to voters: At this time, please vote with the assumption that these patients do not have acute uveitis or IBD, as separate PICO questions focus on those clinical scenarios.*

Summary: This PICO question was directly addressed by 24 RCTs (28 publications). Most studies were placebo-controlled without an active comparator, however, 1 prospective study without clear randomization compared etanercept with thalidomide plus sulfasalazine (Xiao 2015)[23]. One RCT compared infliximab plus methotrexate to methotrexate alone (Marzo 2005)[24], and 1 open-label RCT compared golimumab to pamidronate (Mok 2015)[25]. Approximately half of the studies included in this PICO question constituted new evidence not included in the 2015 Guideline.

Studies directly addressing this PICO included the following TNFis: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Adalimumab was addressed by 3 RCTs. Certolizumab pegol was addressed in one RCT (2 publications). Etanercept was addressed by 8 RCTs (9 publications) and 1 cohort study. Golimumab was addressed in 4 RCTs (5 publications). Infliximab was addressed in 6 RCTs. Statistically significant between group differences favoring TNFi were reported for most outcomes including ASAS 20/40/partial remission, ASDAS, BASDAI, BASFI, pain, patient/physician global VAS, and SI joint/spine scores. No statistically significant findings were reported for two outcomes (MASES, 68-joint tender joint count) with limited evidence.

Overall quality of evidence for all critical outcomes: High

### Table 1: TNFi_vs_no TNFi for improving outcomes in adults with active AS despite NSAIDs

**Table 1: TNFi_vs_no TNFi for improving outcomes in adults with active AS despite NSAIDs (range 8 to 48 weeks; majority are 12-16 weeks)**
**Bibliography: Tam[26]; Landewe[27]; Sieper[28]; Sieper[29]; Song[30]; Inman 2008[31]; Lambert 2007[32,33]; van der Heijde 2006 [33] [2260]; Marzo-Ortega 2005[24]; Davis 2003[34]; Brandt[35]; Braun[36]; Deodhar 2018[37]; Mok 2015[25]; Dougados[38]; Huang[39]; Hu 2015[40]; Braun[41]; Dougados[42]; Barkham[43]; Inman 2010[44]; van der Heijde[45]; van der Heijde 2005[46]; Calin 2004[47]; Gorman 2002[48]; Bao 2014[49]; Xiao 2015[23]; Braun 2012[50]; Poddubnyy 2016[51]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With placebo | With TNFi_vs_no TNFi | | Risk with placebo | Risk difference with TNFi_vs_noTNFi |
| **ASAS20** | | | | | | | | | | | |
| 3430 (19 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 411/1297 (31.7%) | 1390/2133 (65.2%) | **OR 3.99** (3.27 to 4.88) | 317 per 1,000 | **332 more per 1,000** (286 more to 377 more) |
| **ASAS40** | | | | | | | | | | | |
| 2526 (12 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 178/881 (20.2%) | 835/1645 (50.8%) | **OR 4.34** (3.25 to 5.81) | 202 per 1,000 | **322 more per 1,000** (249 more to 393 more) |
| **ASDAS** | | | | | | | | | | | |
| 884 (6 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 347 | 537 | - | - | MD **1.32 lower** (1.53 lower to 1.11 lower) |
| **ASAS partial remission** | | | | | | | | | | | |
| 2697 (11 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 74/977 (7.6%) | 452/1720 (26.3%) | **OR 4.45** (3.07 to 6.46) | 76 per 1,000 | **191 more per 1,000** (125 more to 270 more) |
| **BASDAI** | | | | | | | | | | | |

**Table 1: TNFi_vs_no TNFi for improving outcomes in adults with active AS despite NSAIDs (range 8 to 48 weeks; majority are 12-16 weeks)**
**Bibliography: Tam[26]; Landewe[27]; Sieper[28]; Sieper[29]; Song[30]; Inman 2008[31]; Lambert 2007[32,33]; van der Heijde 2006 [33] [2260]; Marzo-Ortega 2005[24]; Davis 2003[34]; Brandt[35]; Braun[36]; Deodhar 2018[37]; Mok 2015[25]; Dougados[38]; Huang[39]; Hu 2015[40]; Braun[41]; Dougados[42]; Barkham[43]; Inman 2010[44]; van der Heijde[45]; van der Heijde 2005[46]; Calin 2004[47]; Gorman 2002[48]; Bao 2014[49]; Xiao 2015[23]; Braun 2012[50]; Poddubnyy 2016[51]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1475 (15 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 587 | 888 | - | - | MD **1.15 lower** (1.57 lower to 0.72 lower) |
| **BASFI** | | | | | | | | | | | |
| 2672 (17 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 1040 | 1632 | - | - | MD **4.37 lower** (7.85 lower to 0.89 lower) |
| **MASES** | | | | | | | | | | | |
| 659 (2 RCTs) | not serious | not serious | not serious | serious [a] | none | ⊕⊕⊕◯ MODERATE | 222 | 437 | - | - | MD **0.92 lower** (1.9 lower to 0.06 higher) |
| **PGA** | | | | | | | | | | | |
| 1051 (7 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 394 | 657 | - | - | MD **1.62 lower** (2.28 lower to 0.96 lower) |
| **PTGA** | | | | | | | | | | | |
| 965 (6 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 349 | 616 | - | - | MD **1.94 lower** (2.99 lower to 0.89 lower) |
| **SF-36, physical component score** | | | | | | | | | | | |
| 812 (5 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 316 | 496 | - | - | MD **3.26 higher** (0.87 higher to 5.64 higher) |
| **Total back pain** | | | | | | | | | | | |
| 1094 (8 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 412 | 682 | - | - | MD **2.17 lower** (2.96 lower to 1.38 lower) |
| **66-joint swollen joint count** | | | | | | | | | | | |
| 722 (2 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 238 | 484 | - | - | MD **1.09 lower** (1.84 lower to 0.34 lower) |
| **68-joint tender joint count** | | | | | | | | | | | |
| 722 (2 RCTs) | not serious | not serious | not serious | not serious | serious [a] | none | ⊕⊕⊕◯ MODERATE | 238 | 484 | - | - | MD **0.76 lower** (1.97 lower to 0.45 higher) |
| **Pain** | | | | | | | | | | | |
| 1502 (4 RCTs) | not serious | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 548 | 954 | - | - | MD **20.73 lower** (29.75 lower to 11.71 lower) |
| **Berlin score, mean change 12wks** | | | | | | | | | | | |
| 163 (1 RCTs) | not serious | not serious | not serious | not serious | serious | none | ⊕⊕⊕◯ MODERATE | 54 | 109 | - | - | **MD 3.1 lower** (4.6 lower to 1.6 lower) |
| **Serious adverse events** | | | | | | | | | | | |
| 4001 (22 RCTs) | not serious | not serious | not serious | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 40/1512 (2.6%) | 72/2489 (2.9%) | **OR 1.02** (0.68 to 1.54) | 26 per 1,000 | **1 more per 1,000** (8 fewer to 14 more) |
| **Serious infection** | | | | | | | | | | | |
| 2231 (8 RCTs) | not serious | not serious | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 1/763 (0.1%) | 7/1468 (0.4%) | **OR 1.28** (0.35 to 4.63) | 1 per 1,000 | **0 fewer per 1,000** (1 fewer to 5 more) |
| **Myocardial infarction** | | | | | | | | | | | |

**Table 1: TNFi_vs_no TNFi for improving outcomes in adults with active AS despite NSAIDs (range 8 to 48 weeks; majority are 12-16 weeks)**
**Bibliography: Tam[26]; Landewe[27]; Sieper[28]; Sieper[29]; Song[30]; Inman 2008[31]; Lambert 2007[32,33]; van der Heijde 2006 [33] [2260]; Marzo-Ortega 2005[24]; Davis 2003[34]; Brandt[35]; Braun[36]; Deodhar 2018[37]; Mok 2015[25]; Dougados[38]; Huang[39]; Hu 2015[40]; Braun[41]; Dougados[42]; Barkham[43]; Inman 2010[44]; van der Heijde[45]; van der Heijde 2005[46]; Calin 2004[47]; Gorman 2002[48]; Bao 2014[49]; Xiao 2015[23]; Braun 2012[50]; Poddubnyy 2016[51]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 624 (3 RCTs) | not serious | not serious | not serious | serious [c] | none | ⊕⊕⊕◯ MODERATE | 0/223 (0.0%) | 2/401 (0.5%) | **RR 2.10** (0.22 to 19.88) | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |

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

## Explanations

a. 95% CI overlaps the line of no difference.
b. Wide 95% CI
c. Very few events reported. Wide 95% CI overlaps the line of no difference.

## Table 2. Additional RCT Data (all direct evidence; majority not included in Table 1 because SD's and CI's not reported)

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 981, Bao 2014[49] | RCT | 14 weeks | 213 Chinese patients with active AS | GOL vs. placebo | ASAS40: significant difference over baseline at 14 weeks favoring GOL (p<0.001) |
| 1771, Inman 2010[44] | RCT | 12 weeks | 76 patients with active AS | IFX vs. placebo | BASDAI: significant difference over baseline at 12 weeks favoring IFX (-2.1 IFX, -0.7 placebo; p=0.003).<br>BASFI: significant difference over baseline at 12 weeks favoring IFX (-1.8 IFX, -0.4 placebo; p=0.004). |
| 1964, Inman 2008[31] | RCT | 14 weeks | 278 patients with active AS (138 GOL 50 mg, 78 placebo) | GOL vs. placebo | ASAS40: significant difference over baseline at 14 weeks favoring GOL (p<0.001)<br>ASAS partial remission: significant difference over baseline at 14 weeks favoring GOL (p<0.001)<br>Patient's global assessment of disease activity: significant difference over baseline at 14 weeks favoring GOL (media IQR: -2.8 (-5.0 to -1.0) GOL, -0.8 (-2.3 to 0.30) placebo; p<0.001)<br>BASFI, 0-10 scale: significant difference over baseline at 14 weeks favoring GOL (median IQR -1.4 (-3.1 to -0.1) GOL, 0.1 (-1.1 to 1.1) placebo; p<0.001)<br>Patient's assessment of total back pain, 0-10 cm VAS: significant difference over baseline at 14 weeks favoring GOL (median IQR: -3.5 (-5.5 to -0.8) GOL, -0.8 (-3.1 to 0.3) placebo; p<0.001)<br>SF-36 Health Survey, PCS (0-50 scale): significant difference over baseline at 14 weeks favoring GOL (median IQR: 7.3 (1.5 to 15.3) GOL, 2.4 (-1.4 to 7.8) placebo; p<0.001) |
| 2176, Braun 2007[52] | RCT | 12 weeks | 206 pts with active AS (only ETA and placebo arms) | ETA (50 mg/wk) vs. placebo | SF-36: significant difference favoring ETA at 12 weeks. |
| 2098, Lambert 2007[32] | RCT | 12 weeks | 82 patients with active AS | ADA vs. placebo | Mean spine SPARCC score significant difference favoring ADA (median change -6.3, range -34.0 to 2.0 ADA vs. -0.5, range -26.0 to 13.5 placebo; p<0.001).<br>Mean change in SI joint SPARCC score significant difference favoring ADA (median change -0.5, range -22.5 to 2.5 ADA vs. 0.0, range -13.5 to 16.0 placebo; p<0.001). |
| 2240, van der Heijde 2006[45] | RCT | 12 weeks | 206 patients with active AS (in ETA and placebo arms) | ETA (50 mg) vs. placebo | BASFI: significant difference favoring ETA at 12 weeks.<br>BASDAI: significant difference favoring ETA at 12 weeks.<br>PGA: significant difference favoring ETA at 12 weeks.<br>Nocturnal back pain: significant difference favoring ETA at 12 weeks. |
| 2424, van der Heijde 2005[46] | RCT | 24 weeks | 279 patients with active AS | IFX vs. placebo | BASDAI, 0-10: significant difference in median change from baseline to week 24 favoring IFX (median IQR -2.9, -4.9 to -0.9 IFX, -0.4, -1.4 to 0.7 placebo; p<0.001)<br>BASFI, 0-10: significant difference in median change from baseline to week 24 favoring IFX (median IQR -1.7, -3.6 to -0.6 IFX, 0.00, -1.0 to 1.0 placebo; p<0.001)<br>Night pain, 0-10 VAS: significant difference in median change from baseline to week 24 favoring IFX (median IQR -2.9, -5.6 to -0.8 IFX, -0.3, -1.7 to 0.9 placebo; p<0.001)<br>Patient's global assessment, 0-10 VAS: significant difference in median percent change from baseline to week 24 favoring IFX (median IQR 49.2, 11.4 to 77.3 IFX, 6.1, -16.4 to 30.0 placebo; p<0.001) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | SF-36 summary scores, physical component: significant difference in median change from baseline to week 24 favoring IFX (median IQR 10.2, 3.9 to 17.1 IFX, 0.8, -1.9 to 6.0 placebo; p<0.001) |
| 2457, Calin 2004[47] | RCT | 12 weeks | 84 patients with active AS | ETA vs. placebo | Nocturnal and total pain (VAS): significant difference in mean percentage change at 12 weeks favoring ETA ( 43.1% ETA, 6.2% placebo; p=0.000)<br>Patient global assessment (VAS): significant difference in mean percentage change at 12 weeks favoring ETA (37% ETA, 12.6% placebo; p=0.011)<br>BASFI: significant difference in mean percentage change at 12 weeks favoring ETA (35.4 ETA, 3.4 placebo; p=0.000)<br>BASDAI: significant difference in mean percentage change at 12 weeks favoring ETA (43.6% ETA, 13.6% placebo; p=0.001) |

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## PICO 38: In adults with active non-radiographic axial SpA despite treatment with NSAIDs, are TNFi more effective than no treatment with TNFi in improving outcomes?

*Guidance to voters: This is similar to PICO 6, which posed the same question in AS.*

Summary: This PICO question was directly addressed by 6 RCTs (10 publications). (Sieper 2014)[53] did not report results for nr-axSpA separate from than of AS, and hence is excluded). Studies were placebo-controlled without an active comparator.

Studies addressing this PICO evaluated adalimumab (2 studies), certolizumab pegol (1 study), etanercept (1 study), golimumab (1 study), and infliximab (1 study). Studies ranged in size from 39 patients to 213 patients; 4 studies enrolling more than 150 patients. Follow-up was 12 to 26 weeks for the outcomes reported below.

Results indicated statistically significant between group differences favoring TNFi over placebo for most outcomes including ASAS 20/40/partial remission, ASDAS, MASES, joint counts, BASDAI, pain, BASFI, and SPARCC and Berlin spine scores (see Table 1). A statistically significant difference favoring TNFi was also reported for total MRI score at 16 weeks in one study (see Table 2). No statistically significant differences were reported for patient global assessment (3 studies) and SPARCC SI score (1 study). Both outcomes were downgraded for imprecision due to lack of reporting measures of dispersion.

Overall quality of evidence for all critical outcomes: High

### Table 1: TNFi vs. no TNFi

**Table 1: TNFi vs. no TNFi**
**Bibliography: Sieper 2013[29]; Sieper 2015[54]; Haibel 2008[55]; Barkham 2009[56]; Dougados 2014[57]; Maksymowych 2015[58]; Dougados 2017[59]; Dougados 2015[60]; Landewe 2014[61]; van der Heijde 2017[62]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With no TNFi | With TNFi | | Risk with no TNFi | Risk difference with TNFi |
| **ASAS20** | | | | | | | | | | | |
| 788 (5 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 134/376 (35.6%) | 245/412 (59.5%) | **OR 2.65** (1.93 to 3.62) | 356 per 1,000 | **238 more per 1,000** (160 more to 311 more) |
| **ASDAS** | | | | | | | | | | | |
| 332 (2 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 144 | 188 | - | - | MD **1.55 lower** (1.88 lower to 1.22 lower) |
| **ASAS partial remission** | | | | | | | | | | | |
| 412 (4 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 10/184 (5.4%) | 58/228 (25.4%) | **OR 5.39** (2.65 to 10.98) | 54 per 1,000 | **182 more per 1,000** (78 more to 333 more) |
| **MASES** | | | | | | | | | | | |
| 443 (3 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 225 | 218 | - | - | MD **0.7 lower** (0.78 lower to 0.62 lower) |
| **Joint Counts** | | | | | | | | | | | |
| 261 (2 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 133 | 128 | - | - | MD **0.2 higher** (0.16 higher to 0.24 higher) |
| **BASDAI** | | | | | | | | | | | |
| 633 (5 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 297 | 336 | - | - | MD **1.51 lower** (2.55 lower to 0.46 lower) |

**Table 1: TNFi vs. no TNFi**

**Bibliography: Sieper 2013[29]; Sieper 2015[54]; Haibel 2008[55]; Barkham 2009[56]; Dougados 2014[57]; Maksymowych 2015[58]; Dougados 2017[59]; Dougados 2015[60]; Landewe 2014[61]; van der Heijde 2017[62]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pain** | | | | | | | | | | | |
| 446 (3 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 227 | 219 | - | - | MD **0.9 lower** (0.98 lower to 0.82 lower) |
| **BASFI** | | | | | | | | | | | |
| 633 (5 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 297 | 336 | - | - | MD **1.41 lower** (2.49 lower to 0.33 lower) |
| **SF-36 physical component** | | | | | | | | | | | |
| 445 (3 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 226 | 219 | - | - | MD **2.63 higher** (0.2 higher to 5.06 higher) |
| **SPARCC (SI joints)** | | | | | | | | | | | |
| 168 (1 RCT) | not serious | not serious [b] | not serious | serious [c] | none | ⊕⊕⊕◯ MODERATE | 84 | 84 | - | - | **Not estimable** |
| **SPARCC spine score** | | | | | | | | | | | |
| 208 (1 RCT) | not serious | not serious | not serious | serious [d] | none | ⊕⊕⊕◯ MODERATE | 106 | 102 | - | - | SMD **0**.90 **lower** (2.29 lower to 0.49 higher) |
| **Serious adverse events** | | | | | | | | | | | |
| 1043 (6 RCTs) | not serious | not serious | not serious | serious [e] | none | ⊕⊕⊕◯ MODERATE | 6/469 (1.3%) | 7/574 (1.2%) | **OR 1.03** (0.32 to 3.26) | 13 per 1,000 | **0 fewer per 1,000** (9 fewer to 28 more) |
| **Serious infections** | | | | | | | | | | | |
| 224 (1 RCTs) | not serious | not serious | not serious | serious [f] | none | ⊕⊕⊕◯ MODERATE | 1/113 (0.9%) | 0/111 (0.0%) | **RR 0.34** (0.01 to 8.24) | 9 per 1,000 | **6 fewer per 1,000** (9 fewer to 64 more) |

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

## Explanations

a. No measures of dispersion reported in 2 (50%) studies. Wide 95% CI overlaps the line of no difference.
b. Not applicable
c. Single study with no measures of dispersion reported.
d. Single study and 95% CI overlaps the line of no difference.
e. 95% CI overlaps the line of no difference.
f. Single study with very few events reported. 95% CI overlaps the line of no difference.

## Table 2. Observational Data: TNFi vs. no TNFi

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| **EMBARK trial** | | | | | |
| 94, Dougados 2017[59] | Open-label continuation | 104 weeks | 205 adult patients with axial SpA | 50 mg etanercept (ETN), 1/wk All patients (including PBO group switched to open-label ETN after 12 weeks) | Data for patients receiving ETN throughout study:<br>ASAS20 (wk 104): 61 of 81 (75%)<br>ASDAS inactive disease: 48 of 80 patients (60%)<br>BASDAI 50 response: 57 of 81 patients (70%)<br>SAEs: 17 of 224 patients (8%) |
| 611, Maksymowhch 2015[58] | Open-label continuation | 48 weeks | 205 patients with (n=190 completed 48 wks) | 50 mg ETN, 1/wk | ASAS40 (wk 48): 108 of 205 (53%) patients<br>Percentage of patients achieving ASAS20, ASAS 5/6, ASDAS inactive disease and BASDAI50 increased for the two treatment groups (ETN/PBO and ETN continuation) and both groups achieved similar results at week 48<br>SAEs: 4 patients (2%) |
| **RAPID-axSpA Trial** | | | | | |
| 4109, van der Heijde 2018[63] | Dose-blind/open label continuation study | 4 years | 218 patients with nr-axSpA and AS (n=97 with nr-axSpA) | certolizumab pegol (200 mg Q2W or 400 mg Q4W) | Remission (wk 204):<br>69.6% of nr-axSpA patients with BL SPARCC scores ≥2<br>57.3% of nr-axSpA patients with BL Berlin score >2 |
| 89, van der Heijde 2017[62] | Dose-blind open label continuation study | 4 years | 218 patients with nr-axSpA and AS (n=97 with nr-axSpA) | certolizumab pegol (200 mg Q2W or 400 mg Q4W) | Measures at week 204 (observed cases):<br>ASAS20: 49 of 60 (81.7%) nr-axSpA patients<br>BASDAI50: 38 of 60 (63.3%) nr-axSpA patients<br>Mean BASDAI: 2.6 ± 2.2<br>Mean BASFI: 2.2 ± 2.2<br>SAEs: n=32 (22.7%) in nr-axSpA patients |
| 797, Sieper 2015[64] | Dose-blind open label continuation study | 2 years | 218 patients with nr-axSpA and AS (n=97 with nr-axSpA) | certolizumab pegol (200 mg Q2W or 400 mg Q4W) | Measures at week 96 (observed cases):<br>ASAS20: 79.7% nr-axSpA patients<br>ASAS-PR: 43.2% nr-axSpA patients<br>Mean ASDAS: 1.8<br>Mean BASDAI: 2.7<br>Mean BASFI: 2.3<br>SAEs: 41 (13%) |
| **Other trials** | | | | | |
| 1920, Barkham 2009[56] | RCT | 16 weeks | 39 non-radiographic SpA | Infliximab vs. placebo (39 patients underwent MRI) | Statistically significant difference in median (IQR) change in total MRI score at 16 weeks favoring infliximab (-2.00 (-6.25, 0.00) infliximab, 0 (-2.00, 1.50) placebo; p=0.033).<br>SAEs: No serious adverse events. |

## PICO 7: In adults with active AS despite treatment with NSAIDs, is treatment with an oral small molecule more effective than no treatment with an oral small molecule in improving outcomes?

*Guidance to voters: At this time, please vote according to the best evidence for any oral small molecule for any clinical scenario (e.g. concomitant peripheral arthritis). During the voting meeting, we will discuss terminology (oral small molecule, DMARD, slow acting anti rheumatic drug (SAARD), etc) and consider varying the recommendation for individual medications in individual circumstances.*

Summary: This PICO was directly addressed by 17 RCTs.[7-22] Interventional drugs considered for this PICO were tofacitinib in 1 trial, sulfasalazine in 9 trials, methotrexate in 3 trials, leflunomide in 1 trial, pamidronate in 1 trial, thalidomide in 1 trial, and apremilast in 1 trial. New evidence compared to the 2015 guidelines for this PICO question includes two studies [1,2] providing direct evidence: the study with tofacitinib and an additional sulfasalazine study.

- In the one RCT that evaluated tofacitinib (van der Heijde 2017)[65], investigators performed a dose ranging study of 207 patients with active AS. Patients were randomized 1:1:1:1 to placebo or tofacitinib at 2, 5, and 10 mg, twice daily for 12 weeks (outcomes from the 5 mg group included in this report). Tofacitinib at a dose of 5 mg BID demonstrated a significantly greater clinical efficacy versus placebo in reducing symptoms and objective endpoints of active AS in adult patients (ASAS20 response rate 80.8% versus 41.2% for placebo; p<0.001; improved MRI SPARCC SI joint and spine scores with a dose-response). The safety profile was also favorable over 12-weeks.
- Eight of the nine trials that examined the effect of sulfasalazine (see Table 2) were performed before 1996 and thus before the development of contemporary composite scores. Outcome measures were diverse, which precluded the pooling of data for meta-analysis in many instances. In the newly added Khanna-Sharma et al. (Khanna 2017)[66] RCT tested the efficacy of sulfasalazine in 67 adult patients with AS versus placebo over 6 months. Sulfasalazine produced clinically significant improvement in axial symptoms ASDAS (change in ASDAS > 1.1) in 15.1% of placebo and 67.7% in the treatment group (p = 0.001). The mean and standard deviation of the change in ASDAS in treatment group was 1.33 +/- 0.38 (range: 0.9 to 2.3) compared to 0.748 +/- 0.23 (range: 0.4 to 1.3) for placebo. Changes in BASDAI and BASMI were also significantly greater for the treatment group. The older data demonstrated that sulfasalazine had a weak beneficial effect on spinal pain but not on other critical outcome measures, other than poorly defined "episodes of joint symptoms (arthritis or periarthritis)" and ad-hoc "composite peripheral joint scores" (Kirwan 1993; Clegg 1996 )[67,68]. These peripheral joint scores favored sulfasalazine despite no difference in actual tender/swollen joint counts.
- The three studies that compared methotrexate (Table 3) with placebo used weekly doses of 10 mg or less. There was no benefit over placebo for any critical outcomes. A dose of 10 mg weekly is likely suboptimal. However, a cohort study (Haibel 2007)[69] analyzed the efficacy of 20 mg weekly in AS and similarly failed to detect significant benefit, except in peripheral disease.
- The pamidronate study (Table 4) compared two doses of drug without a placebo group. Patients treated with the higher dose had better BASDAI, BASFI, and BASMI responses. There was a statistically non-significant higher rate of arthralgias and myalgias after the first infusion.
- There was no benefit of leflunomide on any outcome measures in one study (Table 5).
- The phosphodiesterase inhibitor apremilast demonstrated improvement in BASFI with trends toward benefit for other outcome measures, but these were not statistically significant (see Table 6). Unpublished results of a Phase 3 study (https://clinicaltrials.gov/ct2/show/results/NCT01583374) are not formally reviewed here.
- The thalidomide study was an unblinded randomized trial that compared the effect of thalidomide with naproxen (and sulfasalazine in a third group) on maintenance of TNF inhibitor-induced treatment responses. Patients on thalidomide had a lower relapse rate. At the same time, significantly more patients in the thalidomide group withdrew due to adverse reactions or were lost to follow-up suggesting significant drug side effects (see Table 7).

Overall, evidence from the 2017 review showed some weak evidence for the use of tofacitinib and sulfasalazine, but otherwise a lack of evidence that treatment with OSMs improves outcomes in AS. However, the small number of trials and of patients included in these studies represent important caveats. Furthermore, methotrexate was used at a dose considered sub-therapeutic for the treatment of rheumatoid arthritis.

Overall quality of evidence for all critical outcomes: Very low to Moderate

## Table 1: Tofa (5mg, 2x/day) compared to PBO, 12 weeks (direct evidence)

Quality of Evidence Across All Critical Outcomes for **tofacitinib**: Low

**Table 1: Tofa (5mg, 2x/day) compared to PBO, 12 weeks (direct evidence)**
**Bibliography: van der Heijde 2017[65]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) With PBO, 16 wks | Study event rates (%) With Tofa (5mg, 2x/day) | Relative effect (95% CI) | Anticipated absolute effects Risk with PBO, 16 wks | Anticipated absolute effects Risk difference with Tofa (5mg, 2x/day) |
| **ASAS20 response, 12 wks** | | | | | | | | | | | |
| 103 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⨁⨁⨁◯ MODERATE | 21/51 (41.2%) | 42/52 (80.8%) | **OR 6.00** (2.47 to 14.57) | 412 per 1,000 | **396 more per 1,000** (222 more to 499 more) |
| **ASAS40 response, 12 wks** | | | | | | | | | | | |
| 103 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⨁⨁⨁◯ MODERATE | 10/51 (19.6%) | 24/52 (46.2%) | **OR 3.51** (1.46 to 8.48) | 196 per 1,000 | **265 more per 1,000** (67 more to 478 more) |
| **ASAS partial remission, 12 wks** | | | | | | | | | | | |
| 103 (1 RCT) | not serious | not serious [a] | not serious | serious [c] | none | ⨁⨁⨁◯ MODERATE | 6/51 (11.8%) | 10/52 (19.2%) | **OR 1.79** (0.60 to 5.34) | 118 per 1,000 | **75 more per 1,000** (44 fewer to 298 more) |
| **BASFI (LS mean change), 12 wks** | | | | | | | | | | | |
| 103 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⨁⨁⨁◯ MODERATE | 51 | 52 | - | - | MD **1 lower** (1.83 lower to 0.17 lower) |
| **BASDAI (LS mean change), 12 wks** | | | | | | | | | | | |
| 103 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⨁⨁⨁◯ MODERATE | 51 | 52 | - | - | MD **1 lower** (1.83 lower to 0.17 lower) |
| **ASDAS (LS mean change), 12 wks** | | | | | | | | | | | |
| 103 (1 RCT) | not serious | not serious [a] | not serious | serious [d] | none | ⨁⨁⨁◯ MODERATE | 51 | 52 | - | - | MD **0.7 lower** (0.98 lower to 0.42 lower) |
| **SPARCC SI joint (LS mean change), 12 wks** | | | | | | | | | | | |
| 103 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⨁⨁⨁◯ MODERATE | 51 | 52 | - | - | MD **2.4 lower** (4.62 lower to 0.18 lower) |
| **SPARCC spine (LS mean change), 12 wks** | | | | | | | | | | | |
| 103 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⨁⨁⨁◯ MODERATE | 51 | 52 | - | - | MD **5.4 lower** (8.45 lower to 2.35 lower) |
| **Berlin score (LS mean change), 12 wks** | | | | | | | | | | | |
| 103 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⨁⨁⨁◯ MODERATE | 51 | 52 | - | - | MD **1.8 lower** (2.91 lower to 0.69 lower) |

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

### Explanations

a. Not applicable; single study.
b. Data from single study with limited enrollment; wide 95% CI.
c. Data from single study; wide 95% CI spans line of no difference.
d. Data from single study with limited enrollment.

**Table 2. Data for sulfasalazine [Bibliography: ][66-68,70-75]**

Quality of Evidence Across All Critical Outcomes for **sulfasalazine**: Moderate

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency ($I^2$) | Indirectness | Imprecision | Other considerations | Sulfasalazine | Control | Relative (95% CI) | Absolute | | |
| **Health Status: ASDAS (mean change, 6 mo)** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | no serious inconsistency | no serious indirectness | serious[3] | none | 31 | 33 | - | MD **0.58 higher** (0.42 higher to 0.74 higher) | ⊕⊕⊕◯ MODERATE | IMPORTANT |
| **Health Status: BASDAI (mean change, 6 mo)** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | no serious inconsistency | no serious indirectness | serious[3] | none | 31 | 33 | - | MD **1.82 higher** (1.34 higher to 2.3 higher) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Health Status: BASMI (mean change, 6 mo)** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | no serious inconsistency | no serious indirectness | serious[3] | none | 31 | 33 | - | MD **1.78 higher** (1.35 higher to 2.21 higher) | ⊕⊕⊕◯ MODERATE | IMPORTANT |
| **Health Status: Pain (axial) (follow-up median 31 weeks; measured with: VAS; Better indicated by lower values)** | | | | | | | | | | | | |
| 6 | randomized trials | serious[1] | no serious inconsistency (1%) | no serious indirectness | no serious imprecision | none | 264 | 262 | - | MD 1.84 lower (3.44 to 0.24 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Stiffness (follow-up median 36 weeks; measured with: duration (hours) or VAS; Better indicated by lower values)** | | | | | | | | | | | | |
| 5 | randomized trials | serious[1] | serious (70%) | no serious indirectness | no serious imprecision | none | 241 | 238 | - | MD 0.65 lower (1.73 lower to 0.42 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Health Status: Physical Exam/Joint Counts (follow-up median 30 months; measured with: joint score; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomized trials | serious[1] | no serious inconsistency (0%) | no serious indirectness | no serious imprecision | none | 154 | 157 | - | MD 0.9 lower (2.95 lower to 1.14 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Acute Phase Reactants (follow-up median 25 weeks; measured with: CRP or ESR; Better indicated by lower values)** | | | | | | | | | | | | |
| 6 | randomized trials | serious[1] | serious (65%) | no serious indirectness | no serious imprecision | none | 257 | 259 | - | MD 0.07 lower (0.36 lower to 0.23 higher) | ⊕⊕OO LOW | NOT IMPORTANT |
| **Functional Status: DFI (follow-up median 30 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomized trials | serious[2] | no serious inconsistency (0%) | no serious indirectness | no serious imprecision | none | 154 | 157 | - | MD 0.21 lower (1.21 lower to 0.8 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Functional Status: ROM (follow-up median 36 weeks; measured with: Schober's test; Better indicated by higher values)** | | | | | | | | | | | | |
| 5 | randomized trials | serious[1] | no serious inconsistency (0%) | no serious indirectness | no serious imprecision | none | 249 | 249 | - | MD 0.01 lower (0.2 lower to 0.18 higher) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Health Status: Sleep disturbance (follow-up median 32 weeks)** | | | | | | | | | | | | |
| 2 | randomized trials | serious[2] | no serious inconsistency (0%) | no serious indirectness | no serious imprecision | none | 11/35 (31.4%) | 13/33 (39.4%) | OR 0.71 (0.26 to 1.93) | 78 fewer per 1000 (from 249 fewer to 163 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Tender Joint Count (follow-up median 26 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 43 | 42 | - | MD 0.4 lower (1.04 lower to 0.24 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Swollen Joint Count (follow-up median 26 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 43 | 42 | - | MD 0 higher (0.28 lower to 0.28 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Overall responders % (follow-up median 36 weeks; assessed with: improvement in 2/4 domains)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 50/131 (38.2%) | 48/133 (36.1%) | OR 1.09 (0.66 to 1.8) | 20 more per 1000 (from 89 fewer to 143 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Physician global % responders (follow-up median 26 weeks; assessed with: 5-point rating scale)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 70/131 (53.4%) | 74/133 (55.6%) | OR 0.91 (0.56 to 1.49) | 23 fewer per 1000 (from 144 fewer to 95 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Patient global % responders (follow-up median 26 weeks; assessed with: 5-point rating scale)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 53/131 (40.5%) | 56/133 (42.1%) | OR 0.93 (0.57 to 1.53) | 18 fewer per 1000 (from 128 fewer to 106 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Morning stiffness % responders (follow-up median 26 weeks; assessed with: VAS)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 64/131 (48.9%)<br><br>44.4% | 59/133 (44.4%)<br><br>44.4% | OR 1.2 (0.74 to 1.94) | 45 more per 1000 (from 73 fewer to 164 more)<br><br>45 more per 1000 (from 73 fewer to 164 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Back pain % responders (follow-up median 26 weeks)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 31/131 (23.7%) | 36/133 (27.1%) | OR 0.84 (0.48 to 1.46) | 33 fewer per 1000 (from 119 fewer to 81 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Joint pain (follow-up median 48 weeks; measured with: VAS; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 32 | 30 | - | MD 0 higher (unable to calculate CI) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Joint swelling (follow-up median 48 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 131 | 133 | - | MD 0.3 higher (1.05 lower to 1.65 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Dactylitis score (follow-up median 48 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 131 | 133 | - | MD 0.1 higher (0.04 lower to 0.24 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Enthesitis score (follow-up median 48 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 131 | 133 | - | MD 0.3 higher (0.94 lower to 1.54 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Serious Adverse Event: all combined (study discontinuation) (follow-up median 36 weeks)** | | | | | | | | | | | | |
| 7 | randomized trials | serious[1] | no serious inconsistency (0%) | no serious indirectness | no serious imprecision | none | 42/306 (13.7%) | 30/309 (9.7%) | OR 1.52 (0.91 to 2.55) | 43 more per 1000 (from 8 fewer to 118 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Adverse Event: GI (follow-up median 36 weeks)** | | | | | | | | | | | | |
| 7 | randomized trials | serious[1] | serious (25%) | no serious indirectness | no serious imprecision | none | 18/306 (5.9%) | 16/309 (5.2%) | OR 1.52 (0.91 to 2.55) | 25 more per 1000 (from 4 fewer to 70 more) | ⊕⊕OO LOW | IMPORTANT |

[1] Randomization and blinding poorly described in several studies.
[2] Randomization poorly described.
[3] Data from single study with small enrollment.

## Table 3. Data for methotrexate (unchanged from 2015 Guideline) [Bibliography: ][69,76-78]

Quality of Evidence Across All Critical Outcomes for **methotrexate**: Low

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency ($I^2$)** | **Indirectness** | **Imprecision** | **Other considerations** | **Methotrexate** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Health Status: BASDAI (follow-up median 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomized trials | no serious risk of bias | serious (35%) | serious[1] | no serious imprecision | none | 29 | 34 | - | MD 0.39 higher (0.69 lower to 1.47 higher) | ⊕⊕OO LOW | CRITICAL |
| **Continued on next page**<br>**Health Status: Pain (follow-up median 38 weeks; measured with: VAS; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomized trials | serious[2] | no serious inconsistency (0%) | serious[1] | no serious imprecision | none | 43 | 43 | - | MD 0.76 lower (2.02 lower to 0.49 higher) | ⊕⊕OO LOW | CRITICAL |
| **Health Status: Stiffness (follow-up median 24 weeks; measured with: VAS; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 17 | 18 | - | MD 6 higher (12.35 lower to 24.35 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Acute Phase Reactants (follow-up median 38 weeks; measured with: CRP; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomized trials | serious[2] | no serious inconsistency (0%) | serious[1] | no serious imprecision | none | 38 | 41 | - | MD 0.13 higher (0.27 lower to 0.54 higher) | ⊕⊕OO LOW | NOT IMPORTANT |
| **Functional Status: BASFI (follow-up median 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 17 | 18 | - | MD 0.3 higher (1.03 lower to 1.63 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **HAQ-S (follow-up median 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 17 | 18 | - | MD 0 higher (0.3 lower to 0.3 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Functional Status: DFI (follow-up median 52 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | Serious[3,4] | no serious inconsistency | serious[1] | no serious imprecision | none | 26 | 25 | - | MD 4.41 higher (0.27 lower to 9.09 higher) | ⊕⊕OO LOW | CRITICAL |
| **Functional Status: BASMI (follow-up median 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[3] | no serious inconsistency | serious[1] | no serious imprecision | none | 12 | 16 | - | MD 0.25 higher (0.91 lower to 1.41 higher) | ⊕⊕OO LOW | NOT IMPORTANT |
| **Health Status: Composite score (follow-up median 24 weeks; assessed with: non-validated composite score, improvement of 20% or more in 5/7 domains)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 9/17 (52.9%) | 3/18 (16.7%) | OR 5.62 (1.18 to 26.85) | 363 more per 1000 (from 24 more to 676 more) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Health Status: Patient global (follow-up median 38 weeks; measured with: VAS or 5-point rating scale; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomized trials | serious[2] | no serious inconsistency (0%) | serious[1] | no serious imprecision | none | 43 | 43 | - | MD 0.31 higher (0.41 lower to 1.02 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Health Status: Physician global (follow-up median 38 weeks; measured with: VAS or 5-point rating scale; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomized trials | serious[2] | serious (70%) | serious[1] | no serious imprecision | none | 43 | 43 | - | MD 4.95 lower (16.95 to 6.60 higher) | ⊕OOO VERY LOW | IMPORTANT |
| **Health Status: Enthesis index (follow-up median 52 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[4] | no serious inconsistency | serious[1] | no serious imprecision | none | 26 | 25 | - | MD 1.27 lower (4.6 lower to 2.06 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Spondylitis index (follow-up median 52 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[4] | no serious inconsistency | serious[1] | no serious imprecision | none | 26 | 25 | - | MD 0.07 lower (1.51 lower to 1.37 higher) | ⊕⊕OO LOW | IMPORTANT |

[1] Lower dose than used in clinical practice.
[2] One of two studies not blinded.
[3] Randomization not explained.
[4] Study not blinded.

**Table 4. Data for pamidronate (unchanged from 2015 Guideline) [Bibliography: ][79]**

Quality of Evidence Across All Critical Outcomes for **pamidronate**: Moderate

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency ($I^2$) | Indirectness | Imprecision | Other considerations | Pamidronate | Control | Relative (95% CI) | Absolute | | |
| **Health Status: BASDAI (follow-up median 6 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 41 | 43 | - | MD 1.27 lower (2.05 to 0.49 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Functional Status: BASFI (follow-up median 6 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 41 | 43 | - | MD 1.52 lower (2.09 to 0.95 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Functional Status: BASMI (follow-up median 6 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 41 | 43 | - | MD 0.48 lower (0.9 to 0.06 lower) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Adverse Event: arthralgia/myalgia (follow-up median 6 months)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 28/41 (68.3%) | 20/43 (46.5%) | OR 2.48 (1.02 to 6.03) | 218 more per 1000 (from 5 more to 375 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: BAS-G (follow-up median 6 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 41 | 43 | - | MD 1.06 lower (1.86 to 0.26 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |

[1] No placebo group.

**Table 5. Data for leflunomide (unchanged from 2015 Guideline) [Bibliography: ][80]**

Quality of Evidence Across All Critical Outcomes for **leflunomide**: Moderate

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency ($I^2$) | Indirectness | Imprecision | Other considerations | Leflunomide | Control | Relative (95% CI) | Absolute | | |
| **Health Status: BASDAI (follow-up median 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 30 | 15 | - | MD 0.8 lower (2 lower to 0.5 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Health Status: Pain (follow-up median 24 weeks; measured with: VAS; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 30 | 15 | - | MD 0.9 lower (2.8 lower to 0.9 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Health Status: Acute Phase Reactants (follow-up median 24 weeks; measured with: CRP; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 30 | 15 | - | MD 12.6 higher (5.8 lower to 30.9 higher) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Functional Status: BASFI (follow-up median 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 30 | 15 | - | MD 0.4 higher (0.5 lower to 1.3 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Continued on next page** | | | | | | | | | | | | |
| **Functional Status: BASMI (follow-up median 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 30 | 15 | - | MD 0.3 lower (0.8 lower to 0.1 higher) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Health Status: ASAS20 (follow-up median 24 weeks)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 8/30 (26.7%) | 3/15 (20%) | OR 1.45 (0.32 to 6.53) | 66 more per 1000 (from 126 fewer to 420 more) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Health Status: BAS-G (follow-up median 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 30 | - | - | MD 0.7 lower (2.4 lower to 0.9 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Swollen Joint Count (follow-up median 24 weeks; measured with: 44 joint count; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 30 | 15 | - | MD 0.4 higher (0.1 lower to 0.9 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Physician global (follow-up median 24 weeks; measured with: vas; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 30 | 15 | - | MD 0.2 higher (0.8 lower to 1.1 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Adverse Event: GI** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 17/30 (56.7%) | 5/15 (33.3%) | OR 2.62 (0.72 to 9.54) | 234 more per 1000 (from 69 fewer to 493 more) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Adverse Event: URI** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 5/30 (16.7%) | 4/15 (26.7%) | OR 0.55 (0.12 to 2.45) | 100 fewer per 1000 (from 225 fewer to 204 more) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Adverse Event: dermatitis/prurigo** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 4/30 (13.3%) | 2/15 (13.3%) | OR 1 (0.16 to 6.19) | 0 fewer per 1000 (from 109 fewer to 354 more) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Adverse Event: DVT** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/30 (0%) | 1/15 (6.7%) | OR 0.16 (0.01 to 4.13) | 55 fewer per 1000 (from 66 fewer to 161 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Adverse Event: LFT elevation** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 1/30 (3.3%) | 0/15 (0%) | OR 1.58 (0.06 to 41.03) | - | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Adverse Event: HTN** | | | | | | | | | | | | |
| 1 | randomized trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 1/30 (3.3%) | 0/15 (0%) | OR 1.58 (0.06 to 41.03) | - | ⊕⊕⊕O MODERATE | NOT IMPORTANT |

[1] Randomization not explained.

**Table 6. Data for apremilast (unchanged from 2015 Guideline) [Bibliography: ][81]**

Quality of Evidence Across All Critical Outcomes for **apremilast**: Moderate

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency ($I^2$) | Indirectness | Imprecision | Other considerations | Apremilast | Control | Relative (95% CI) | Absolute | | |
| **Health Status: BASDAI (follow-up median 12 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 17 | 19 | - | MD 0.82 lower (1.79 lower to 0.15 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Health Status: ASDAS (follow-up median 12 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 17 | 19 | - | MD 0.31 higher (0.14 lower to 0.76 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Health Status: Acute Phase Reactants (follow-up median 12 weeks; measured with: CRP; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 17 | 19 | - | MD 3.61 lower (18.33 lower to 11.11 higher) | ⊕⊕⊕⊕ HIGH | NOT IMPORTANT |
| **Functional Status: BASFI (follow-up median 12 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 17 | 19 | - | MD 1.46 lower (2.62 to 0.3 lower) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Functional Status: BASMI (follow-up median 12 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 17 | 19 | - | MD 0.3 lower (0.87 lower to 0.27 higher) | ⊕⊕⊕⊕ HIGH | NOT IMPORTANT |
| **Health Status: BAS-G (follow-up median 12 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 17 | 19 | - | MD 1.19 lower (2.88 lower to 0.5 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Functional Status: FACIT-F (follow-up median 12 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 17 | 19 | - | MD 4.31 higher (4.26 lower to 12.88 higher) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Health Status: ASAS20 (follow-up median 12 weeks)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 6/17 (35.3%) | 3/19 (15.8%) | OR 2.91 (0.6 to 14.18) | 195 more per 1000 (from 57 fewer to 569 more) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Health Status: ASAS40 (follow-up median 12 weeks)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 4/17 (23.5%) | 1/19 (5.3%) | OR 5.54 (0.55 to 55.49) | 183 more per 1000 (from 23 fewer to 702 more) | ⊕⊕OO LOW | NOT IMPORTANT |
| **Health Status: ASAS5/6 (follow-up median 12 weeks)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 3/17 (17.6%) | 1/19 (5.3%) | OR 3.86 (0.36 to 41.2) | 124 more per 1000 (from 33 fewer to 643 more) | ⊕⊕OO LOW | NOT IMPORTANT |
| **Health Status: Night pain (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 17 | 19 | - | MD 0.58 lower (2.47 lower to 1.31 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Adverse Event: headache** | | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 8/19 (42.1%) | 5/19 (26.3%) | OR 2.04 (0.52 to 8) | 158 more per 1000 (from 107 fewer to 478 more) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Continued on next page**<br>**Adverse Event: loose stools** | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 5/19 (26.3%) | 2/19 (10.5%) | OR 3.04 (0.51 to 18.11) | 158 more per 1000 (from 49 fewer to 575 more) | ⊕⊕⊕O MODERATE | NOT IMPORTANT |
| **Adverse Event: elevated serum amylase** | | | | | | | | | | | |
| 1 | randomized trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 2/19 (10.5%) | 0/19 (0%) | OR 5.57 (0.25 to 124.19) | - | ⊕⊕OO LOW | NOT IMPORTANT |

[1] Wide CI.

**Table 7. Data for thalidomide (unchanged from 2015 Guideline) [Bibliography: ][82]**

Quality of Evidence Across All Critical Outcomes for **thalidomide**: Very Low

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency ($I^2$)** | **Indirectness** | **Imprecision** | **Other considerations** | **Thalidomide** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Recurrence rate (follow-up median 1 years)** | | | | | | | | | | | | |
| 1 | randomized trials | very serious[1,2] | no serious inconsistency | serious[3] | no serious imprecision | none | 25/37 (67.6%) | 33/37 (89.2%) | OR 0.25 (0.07 to 0.88) | 218 fewer per 1000 (from 13 fewer to 526 fewer) | ⊕OOO VERY LOW | IMPORTANT |
| **Adverse Event: Discontinuation or lost to follow-up (follow-up median 1 years)** | | | | | | | | | | | | |
| 1 | randomized trials | very serious[1,2] | no serious inconsistency | serious[3] | no serious imprecision | none | 7/37 (18.9%) | 0/37 (0%) | OR 18.44 (1.01 to 335.96) | - | ⊕OOO VERY LOW | IMPORTANT |

[1] Study not blinded.
[2] Randomization not explained.
[3] Maintenance of clinical benefit after prior TNF inhibitor therapy.

## PICO 39: In adults with active non-radiographic axial SpA despite treatment with NSAIDs, is treatment with an oral small molecule more effective than no treatment with an oral small molecule in improving outcomes?

*Guidance to voters: This is similar to PICO 7, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any studies.

Overall quality of evidence for all critical outcomes: Very Low

**PICO 8: In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, is treatment with a non-TNFi biologic more effective than treatment with an oral small molecule in improving outcomes?**

*Guidance to voters: At this time, please vote according to the best evidence for secukinumab (non-TNFi biologic) versus sulfasalazine (OSM). Keep in mind contraindications that might sway you towards one therapy vs. another (e.g. infection risk). Other comparisons between agents (e.g. secukinumab vs. tofacitinib) will be addressed during the in-person voting meeting by voting on specific pair-wise comparisons in the context of specific TNFi contraindications, rather than the general concept of non-TNFi vs. OSM.*

Summary: This PICO question was not directly addressed by any study. Indirect evidence for this PICO may be derived by qualitatively comparing the clinical responses among patients who were treated with OSMs (PICO 7, which contains data regarding sulfasalazine) or secukinumab (PICO 58, which contains data from a multiple RCTs of secukinumab vs. placebo), and other non-TNFi biologics, including anti-IL6 receptor antagonists (see Table below). Since the 2015 guidelines, a single RCT of sarilumab (Sieper 2015)[83] and two RCTs of tocilizumab (Sieper 2015)[84] have been published. None of these RCTs restricted patients to those with contraindications to TNFi.

*For secukinumab vs. tofacitinib comparison (at meeting):* Additional indirect evidence for this PICO was available in a meta-analysis that compared data from a single RCT of tofacitinib with data from two RCTs of secukinumab (Ungprasert 2017)[16], however, subjects in these studies were not specifically selected due to contraindications to TNFi and the meta-analysis only included two of the secukinumab RCTs. The meta-analysis was not able to identify statistically significant differences in ASAS20 between tofacitinib and secukinumab using these very limited data. Comparisons between other non-TNFi biologics and OSMs have not been studied formally.

Of note, the new data for sarilumab and tocilizumab did not demonstrate benefit in clinical outcomes compared with placebo.
Data regarding abatacept, ustekinumab, rituximab are reproduced below from the 2015 guidelines. *[Results for phase 3 ustekinumab study are available at ClinicalTrials.gov, but were not published or formally considered in this evidence report: https://clinicaltrials.gov/ct2/show/results/NCT02437162]*

Overall quality of evidence for all critical outcomes: Low

## Table 1. IL-6 receptor antagonists compared to placebo for active AS

Quality of Evidence Across All Critical Outcomes for **IL-6 inhibitors**: Low

**Table 1. IL-6 receptor antagonists compared to placebo for active AS**
**Bibliography: Sieper 2015[83]; Sieper 2015[84]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall certainty of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| | | | | | | | **With placebo, 12 wk** | **With IL-6 receptor antagonists** | | **Risk with placebo, 12 wk** | **Risk difference with IL-6 receptor antagonists** |
| ASAS20 response, 12w | | | | | | | | | | | |
| 202 (2 RCTs) | not serious | not serious | serious [a] | serious [b] | none | ⨁⨁◯◯ LOW | 26/101 (25.7%) | 38/101 (37.6%) | **OR 1.74** (0.95 to 3.17) | 257 per 1,000 | **119 more per 1,000** (10 fewer to 266 more) |
| Change ASAS back pain, 12w | | | | | | | | | | | |
| 100 (1 RCT) | not serious | not serious [c] | serious [a] | serious [d] | none | ⨁⨁◯◯ LOW | 50 | 50 | - | - | MD **0.8 lower** (1.57 lower to 0.03 lower) |
| Change ASAS Physical function, 12w | | | | | | | | | | | |
| 100 (1 RCT) | not serious | not serious [c] | serious [a] | serious [e] | none | ⨁⨁◯◯ LOW | 50 | 50 | - | - | MD **0.5 lower** (1.12 lower to 0.12 higher) |
| ASAS partial remission, 12w | | | | | | | | | | | |
| 102 (1 RCT) | not serious | not serious [c] | serious [a] | serious [f] | none | ⨁⨁◯◯ LOW | 1/51 (2.0%) | 0/51 (0.0%) | **OR 0.33** (0.01 to 8.21) | 20 per 1,000 | **13 fewer per 1,000** (19 fewer to 121 more) |
| ASDAS score change, 12w | | | | | | | | | | | |
| 100 (1 RCT) | not serious | not serious [c] | serious [a] | serious [d] | none | ⨁⨁◯◯ LOW | 50 | 50 | - | - | MD **1.2 lower** (1.52 lower to 0.88 lower) |
| BASDAI score change, 12w | | | | | | | | | | | |
| 100 (1 RCT) | not serious | not serious [c] | serious [a] | serious [e] | none | ⨁⨁◯◯ LOW | 50 | 50 | - | - | MD **0.3 lower** (0.99 lower to 0.39 higher) |
| BASMI score change, 12w | | | | | | | | | | | |
| 100 (1 RCT) | not serious | not serious [c] | serious [a] | serious [e] | none | ⨁⨁◯◯ LOW | 50 | 50 | - | - | MD **0** (0.29 lower to 0.29 higher) |
| SAEs or AEs causing discontinuation, 12w | | | | | | | | | | | |
| 201 (2 RCTs) | not serious | not serious | serious [a] | serious [g] | none | ⨁⨁◯◯ LOW | 0/101 (0.0%) | 8/100 (8.0%) | **OR 9.11** (1.11 to 74.94) | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| Infections/infestations, 12w | | | | | | | | | | | |
| 100 (1 RCT) | not serious | not serious [c] | serious [a] | serious [f] | none | ⨁⨁◯◯ LOW | 9/50 (18.0%) | 14/50 (28.0%) | **OR 1.77** (0.69 to 4.58) | 180 per 1,000 | **100 more per 1,000** (48 fewer to 321 more) |
| Death, 12w | | | | | | | | | | | |
| 102 (1 RCT) | not serious | not serious [c] | serious [a] | serious [h] | none | ⨁⨁◯◯ LOW | 0/51 (0.0%) | 0/51 (0.0%) | not estimable | 0 per 1,000 | not estimable |

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

### Explanations

a. Indirect comparison: not comparing OSM vs. placebo.
b. 95% CI spans line of no difference.
c. Not applicable; single study.
d. Single study; moderate-sized enrollment.
e. Single study; moderately sized enrollment; 95% CI spans line of no difference.
f. Single study; wide 95%CI spanning line of no difference.
g. Low event rate; extremely wide 95% CI.
h. Low event rate.

**Table 2. Data for abatacept (unchanged from 2015 Guideline) [Bibliography: ][85,86]**

Quality of Evidence Across All Critical Outcomes for **abatacept**: Very Low

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency ($I^2$) | Indirectness | Imprecision | Other considerations | Abatacept | Control | Relative (95% CI) | Absolute | | |
| **Health Status: BASDAI (follow-up 3 months; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | observational studies | very serious[1] | no serious inconsistency (NC) | very serious[2] | no serious imprecision | none | 20 | - | - | MD .3 lower (unable to calculate CI) | ⊕OOO VERY LOW | CRITICAL |
| **Health Status: Pain (follow-up 3 months; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 5 | - | - | MD 0.02 lower (unable to calculate CI) | ⊕OOO VERY LOW | CRITICAL |
| **Health Status: ROM – Schober's test (cm) (follow-up 3 months; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 5 | - | - | not pooled | ⊕OOO VERY LOW | IMPORTANT |
| **Health Status: ASDAS (follow-up 3 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 15 | - | - | MD 0.1 higher (unable to calculate CI) | ⊕OOO VERY LOW | IMPORTANT |
| **Health Status: Acute Phase Reactants - CRP (mg/L) (follow-up 3 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | observational studies | very serious[1] | no serious inconsistency (NC) | very serious[2] | no serious imprecision | none | 20 | - | - | not pooled | ⊕OOO VERY LOW | NOT IMPORTANT |
| **Functional Status: BASFI (follow-up 3 months; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | observational studies | very serious[1] | no serious inconsistency (NC) | very serious[2] | no serious imprecision | none | 20 | - | - | not pooled | ⊕OOO VERY LOW | CRITICAL |
| **Functional Status: BASMI (follow-up 3 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 15 | - | - | not pooled | ⊕OOO VERY LOW | NOT IMPORTANT |

[1] Small sample size; no control

[2] Indirect comparison: does not directly address non-TNFi versus SAARD

**Table 3. Data for ustekinumab (unchanged from 2015 Guideline) [Bibliography: ][87]**

Quality of Evidence Across All Critical Outcomes for **ustekinumab**: Very Low

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Ustekinumab | Control | Relative (95% CI) | Absolute | | |
| **Health Status: BASDAI (follow-up 24 weeks; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | strong association[2] | 20 | - | - | MD 2.3 lower (5.3 lower to 1.3 higher)[3] | ⊕⊕OO LOW | CRITICAL |
| **Health Status: Pain (follow-up 24 weeks; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | strong association[2] | 20 | - | - | MD 3.2 lower (5.6 to 0.8 lower) | ⊕⊕OO LOW | CRITICAL |
| **Health Status: ASDAS (follow-up 24 weeks; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | strong association[2] | 20 | - | - | MD 1 lower (3 lower to 1.2 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Health Status: Acute Phase Reactants - CRP (mg/L) (follow-up 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | serious[4] | none | 20 | - | - | MD 0.5 higher (unable to calculate CI) | ⊕OOO VERY LOW | NOT IMPORTANT |
| **Health Status: Inflammation on Imaging (follow-up 24 weeks; measured with: MRI-sacroiliac osteitis score; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | serious[5] | none | 17 | - | - | MD 2.2 lower (5.4 lower to 4.6 higher) | ⊕OOO VERY LOW | NOT IMPORTANT |
| **Health Status: ASQOL (follow-up 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | strong association[2] | 20 | - | - | MD 4.3 lower (9.4 lower to 3.7 higher) | ⊕⊕OO LOW | CRITICAL |
| **Functional Status: BASFI (follow-up 24 weeks; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | strong association[2] | 20 | - | - | MD 2.3 lower (5.3 lower to 2.3 higher) | ⊕⊕OO LOW | CRITICAL |
| **Functional Status: BASMI (follow-up 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 20 | - | - | MD 0.4 lower (1.6 lower to 2.2 higher) | ⊕OOO VERY LOW | NOT IMPORTANT |
| **Health Status: ASAS40 (follow-up 24 weeks)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | strong association[2] | 13/20 (65%) | - | 41 to 85 | - | ⊕⊕OO LOW | NOT IMPORTANT |
| **Health Status: BASDAI50 (follow-up 24 weeks)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | strong association[2] | 11/20 (55%) | - | 32 to 77 | - | ⊕⊕OO LOW | NOT IMPORTANT |

[1] Observational study of 20 subjects with 3 dropouts for lack of effect may indicate bias
[2] Large effect seen or p<0.001
[3] 95% CI not available. Rough estimate: 2xSD to give range
[4] Large SD
[5] large SD, p=0.026

**Table 4. Data for rituximab (unchanged from 2015 Guideline) [Bibliography: ][88]**

Quality of Evidence Across All Critical Outcomes for **rituximab**: Very Low

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency ($I^2$) | Indirectness | Imprecision | Other considerations | Rituximab | Control | Relative (95% CI) | Absolute | | |
| **Health Status: BASDAI in TNFi_naïve (follow-up 24 weeks; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | mean 2.0 lower (unable to calculate CI) | ⊕OOO VERY LOW | CRITICAL |
| **Health Status: BASDAI in TNFi exposed (follow-up 24 weeks; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | mean 0.9 lower (unable to calculate CI) | ⊕OOO VERY LOW | CRITICAL |
| **Health Status: Acute Phase Reactants - CRP (mg/L)_TNFi_naïve (follow-up 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | MD 5.5 lower (unable to calculate CI) | ⊕OOO VERY LOW | NOT IMPORTANT |
| **Health Status: Acute Phase Reactants - CRP (mg/L) _TNFi_exposed (follow-up 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | MD 1.4 lower (unable to calculate CI) | ⊕OOO VERY LOW | NOT IMPORTANT |
| **Health Status: ASQOL_TNFi_naïve (follow-up 24 weeks; range of scores: 0-18; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | MD 3.3 lower (unable to calculate CI) | ⊕OOO VERY LOW | CRITICAL |
| **Health Status: ASQOL_TNFi_exposed (follow-up 24 weeks; range of scores: 0-18; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | MD 3.1 lower (unable to calculate CI) | ⊕OOO VERY LOW | CRITICAL |
| **Functional Status: BASFI_TNFi_naïve (follow-up 24 weeks; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | MD 1.3 lower (unable to calculate CI) | ⊕OOO VERY LOW | CRITICAL |
| **Functional Status: BASFI_TNFi_exposed (follow-up 24 weeks; range of scores: 0-10; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | MD 0.5 lower (unable to calculate CI) | ⊕OOO VERY LOW | CRITICAL |
| **Functional Status: BASMI_TNFi_naïve (follow-up 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | MD .4 lower (unable to calculate CI) | ⊕OOO VERY LOW | NOT IMPORTANT |
| **Functional Status: BASMI_TNFi_exposed (follow-up 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | very serious[2] | no serious imprecision | none | 10 | - | - | MD .3 lower (unable to calculate CI) | ⊕OOO VERY LOW | NOT IMPORTANT |

[1] No control

[2] Indirect comparison: does not directly address non-TNFi versus SAARD

**PICO 40: In adults with active non-radiographic axial SpA despite treatment with NSAIDs and who have contraindications to TNFi, is treatment with a non-TNFi biologic more effective than treatment with an oral small molecule in improving outcomes?**

*Guidance to voters: This is similar to PICO 8, which posed the same question in AS.*
*As opposed to PICO 39 (assesses whether you should use tofacitinib or other OSM), this PICO assesses the preference between agents (TNFi vs. tofacitinib).*
Summary: This PICO question was not directly addressed by any study.

Overall quality of evidence for all critical outcomes: Very low

## PICO 9: In adults with active AS despite treatment with the first TNFi agent used, is switching to a different TNFi more effective than adding methotrexate or sulfasalazine in improving outcomes?

*Guidance to voters: This PICO does not distinguish between those that never achieved a response (primary failure of TNFi) and those that achieved a clinical response but lost this effect (secondary failures).*

Summary: This PICO question was not directly addressed by any study. Indirect evidence for this PICO may be derived by qualitatively comparing the clinical responses among patients who switched TNFi due to active disease (four studies summarized below) and those studies of PICO 64 (TNFi co-medication with methotrexate and sulfasalazine). Among the 20+ studies of patients that switched TNFi, only eight reported clinical outcomes (as opposed to the more common outcomes, such as "drug persistence", etc.) and among these eight studies, only four stratified results according to those patients that previously had not adequately responded to TNFi: Lie 2011, Rudwaleit 2010, Paccou 2011 and Ciurea 2016[89-92]. Results for clinical outcomes among these switchers is reported below. In general, BASDAI50 and ASAS 40 responses were in the range of 25-50% at 3 months. Of note, the report by Lie, did not stratify responses by primary (lack of response) and secondary (loss of response) failures.

Based on very limited clinical outcomes from the two small RCTs (summarized in PICO 64), combination treatment with MTX and infliximab appears to have similar efficacy and safety as infliximab monotherapy. However, data from 5 observational studies suggest, in general, greater persistence/lower drug discontinuation with co-treatment, particularly when combining infliximab and methotrexate. This finding was not present in all studies and only one of the observational studies assessed clinical outcomes (finding no difference in BASDAI and ASDAS associated with co-treatment).

Overall quality of evidence for all critical outcomes: Very low

### Table 1. New Observational Data on Switching TNFi

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 779, Ciurea 2016[92] | Observational study | 12 ± 3 mo | 632 patients with axial SpA | Switch to different TNFi following initial TNFi treatment<br>Indirectness: no comparison to MTX or SSZ | ASAS-PR: achieved in 227 of 632 (36%)<br>ASDAS-ESR: achieved in 184 of 632 (29%) |
| 1672, Lie 2011[89] | Observational study | 3 months | 77 switchers | Switch to different TNFi following initial TNFi treatment<br>Indirectness: no comparison to MTX or SSZ | BASDAI 50 response achieved in 25% of pts previously on TNFi ASAS 40 response achieved in 30% of pts previously on TNFi (only 17% at "last observation) |
| 1658, Paccou 2011[91] | Retrospect observational study | 3 months | 377 SpA patients total; 17 switchers with axial disease | Treatment with same TNFi (n=267) or switch to one or more other TNFi (n=99); 99 patients with AS (n=56), PsA, & SpA treated with multiple TNFis<br>Indirectness: no comparison to MTX or SSZ | Following failure of the first TNFi, clinical response based on expert opinion seen in 80.8% (80/99) of pts for 2nd TNFi<br>BASDAI 50 response achieved in 30% of pts for 2nd TNFi |
| 1726, Rudwaleit 2010[90] | Observational study | 12 weeks | 1250 patients with AS;<br>326 with previous TNFi treatment, 924 TNFi naive | TNFi treatment with adalimumab<br>Indirectness: no comparison to MTX or SSZ | BASDAI 50 response achieved in 40.8% of patients previously receiving TNFi therapy<br>ASAS 40 response achieved in 37.7% of patients previously receiving TNFi therapy<br>Rate of SAEs: 4.3% for patients with prior TNFi<br>Rate of serious infections: 0.3% in patients with prior TNFi |

**PICO 41: In adults with active non-radiographic axial SpA despite treatment with the first TNFi agent used, is switching to a different TNFi more effective than adding methotrexate or sulfasalazine in improving outcomes?**

*Guidance to voters: This is similar to PICO 9, which posed the same question in AS. This PICO does not distinguish between those that never achieved a response (primary failure of TNFi) and those that achieved a clinical response but lost this effect (secondary failures).*

Summary: This PICO question was not directly addressed by any study. Very indirect evidence for this PICO may be derived from PICO 9, which qualitatively compares the clinical responses among **AS** patients who switched TNFi due to active disease (four studies) and those studies of PICO 64 (TNFi co-medication with methotrexate and sulfasalazine among **AS** patients). Of the four "switching studies", once included approximately 30% non-radiographic axial SpA (Ciurea 2016)[92] and one may have included an unknown proportion of non-radiographic axial SpA (Paccou 2011)[91]. All the remaining studies from PICO 9 and PICO 64 were comprised of AS patients.

Overall quality of evidence for all critical outcomes: Very low

## PICO 10: In adults with active AS despite treatment with the first TNFi agent used, is switching to a different TNFi more effective than switching to a non-TNFi biologic in improving outcomes?

*Guidance to voters: This PICO does not distinguish between those that never achieved a response (primary failure of TNFi) and those that achieved a clinical response but lost this effect (secondary failures).*
*At this time, please vote according to the best evidence for a second TNFi versus secukinumab (non-TNFi biologic). Keep in mind contraindications that might sway you towards one therapy vs. another (e.g. infection risk). Comparisons between other agents (e.g. sarilumab/tocilizumab, abatacept, ustekinumab, rituximab) will be addressed during the in-person voting meeting by voting on specific pair-wise comparisons, rather than the general concept of second TNFi vs. non-TNFi biologic).*

Summary: This PICO question was not directly addressed by any study. Very indirect evidence for this PICO may be derived by qualitatively comparing the clinical responses among patients who switched TNFi due to active disease (four studies from PICO 9, above) and those studies of secukinumab (PICO 58, which contains data from a multiple RCTs of secukinumab vs. placebo). Data regarding other non-TNFi biologics are summarized in PICO 8, but were generally negative when compared with placebo.

Overall quality of evidence for all critical outcomes: Very low

## PICO 42: In adults with active non-radiographic axial SpA despite treatment with the first TNFi agent used, is switching to a different TNFi more effective than switching to a non-TNFi biologic in improving outcomes?

*Guidance to voters: This is similar to PICO 10, which posed the same question in AS. This PICO does not distinguish between those that never achieved a response (primary failure of TNFi) and those that achieved a clinical response but lost this effect (secondary failures).*
*At this time, please vote according to the best evidence for a second TNFi versus secukinumab (non-TNFi biologic). Keep in mind contraindications that might sway you towards one therapy vs. another (e.g. infection risk). Comparisons between other agents (e.g. sarilumab/tocilizumab, abatacept, ustekinumab, rituximab) will be addressed during the in-person voting meeting by voting on specific pair-wise comparisons, rather than the general concept of second TNFi vs. non-TNFi biologic).*

Summary: This PICO question was not directly addressed by any study. Very indirect evidence for this PICO may be derived from PICO 10, which qualitatively compares the clinical responses among **AS** patients who switched TNFi due to active disease (four studies from PICO 9, above) and those studies of secukinumab (PICO 58, which contains data from multiple RCTs of secukinumab vs. placebo in **AS**). Data regarding other non-TNFi biologics in **AS** are summarized in PICO 8, but were generally negative when compared with placebo. Of the four "switching studies", once included approximately 30% non-radiographic axial SpA (Ciurea 2016)[92] and one may have included an unknown proportion of non-radiographic axial SpA (Paccou 2011)[91]. All the remaining studies from PICO 9 and 58 were comprised of AS patients.

Overall quality of evidence for all critical outcomes: Very low

## PICO 11: In adults with stable AS on treatment with TNFi and NSAIDs, is continuing both medications more effective than continuing treatment with TNFi alone in improving outcomes?

Summary: This PICO question was not directly addressed by any study. This PICO question was very indirectly addressed by one study (Douglas 2014). In this SPARSE study, axSpA patients randomized to etanercept or placebo were advised to taper and discontinue their NSAID if possible. Only 57% of the entire study cohort met modified New York Classification Criteria for AS. For the group randomized to etanercept, 41% were able to achieve an ASAS-NSAID score of 0 (no NSAIDs in the prior 7 days). There was no report of clinical outcomes in those stopping NSAIDs completely, no comparison in outcomes between those off NSAIDs versus patients who continued NSAIDs without any attempt to taper, nor were results stratified by AS vs. nr-axSpA.

The open label, randomized INFAST study (Part 2) addressed this population with stable AS on treatment with TNFi and NSAID. The initial part of INFAST compared infliximab plus naproxen with naproxen alone in moderate-to-severe, active axial SpA[28]. For INFAST part 2 (Sieper 2014)[93], however, infliximab was stopped at 28 weeks of treatment in all subjects, rather than the NSAID.

Overall quality of evidence for all critical outcomes: Very Low

### Table 1. Observational Data

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 808, Dougados 2014[38]<br><br>(indirect evidence) | Observational study (SPARSE) | 8 weeks | 90 patients with active axSpA despite optimal NSAID intake | Taper/discontinuation of NSAID intake following treatment with ETN and NSAID<br>Indirectness: only examines pts who tapered or discontinued NSAIDS; no direct comparison to pts who continue both TNFi and NSAID | Mean change ASAS-NSAID score: 63.9 ± 6.1<br><br>ASAS40: 44% patients<br><br>BASDAI 50: 39% patients |

## PICO 43: In adults with stable non-radiographic axial SpA on treatment with TNFi and NSAIDs, is continuing both medications more effective than continuing treatment with TNFi alone in improving outcomes?

*Guidance to voters: This is similar to PICO 11, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any studies. This PICO question was indirectly addressed by two studies, summarize above in PICO 11. These two studies included 40% and 43% nr-axSpA, but results were not reported specifically for the nr-axSpA group.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 12: In adults with stable AS on treatment with TNFi and an oral small molecule, is continuing both medications more effective than withdrawing one treatment and continuing either TNFi or the oral small molecule alone in improving outcomes?

Summary: This PICO question was not addressed by any study. This PICO question was indirectly addressed by one retrospective study (Nair 2017)[94] of 45 patients that achieved a mean BASDAI of 1.9 (SD 1.1) on a short course of infliximab with methotrexate (91% of cohort) and sulfasalazine (96% of cohort). After 4 infliximab doses the infusions were discontinued, but methotrexate and sulfasalazine were continued. The flare rate (BASDAI≥4) was 20% at 1 year and 40% at 2 years.

Overall quality of evidence for all critical outcomes: Very low

## PICO 44: In adults with stable non-radiographic axial SpA on treatment with TNFi and an oral small molecule, is continuing both medications more effective than withdrawing one treatment and continuing either TNFi or the oral small molecule alone in improving outcomes?

*Guidance to voters: This is similar to PICO 12, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any studies.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 29: In adults with AS and recurrent attacks of uveitis, is treatment with certain biologics more effective than others in improving outcomes?

Summary: This PICO question was not directly addressed by any study. Very indirect evidence to compare TNFi versus secukinumab may be derived by qualitatively comparing the rate of anterior uveitis (AU) in in 7 observational studies that compared rates of uveitis flares between TNFi, one study that pooled data from 4 RCTs and 3 retrospective observational cohorts to compare uveitis flare rates, and the RCTs of secukinumab, which report uveitis flares (Tables 1 and 2, below). The majority of these studies were not performed in patients with a history of uveitis or recurrent uveitis. No studies compared non-TNFi biologics to TNFi biologics. The crude flare rates do not differ between secukinumab and placebo according to the Fischer's Exact Test (see Table 1, below).

In general, AU flare rates were lowest for adalimumab and infliximab compared with etanercept. Compared to periods prior to institution of TNFi, adalimumab and infliximab produced lower AU flare rates, whereas rates with introduction of etanercept remained stable or increased.

A number of observational studies examined uveitis flare rates with a single agent (rather than comparing between agents) in patients with AS (Calvo-rio 2016, Yazgan 2017, Rudwaleit 2016, van Denderen 2014, Sieper 2010, Rudwaleit 2009, Rudwaleit 2016). Because these do not compare results between biologics, they are NOT included in the evidence report.

Overall quality of evidence for all critical outcomes: Low

**Table 1: Summary Evidence on Uveitis Flares from Secondary Analysis of Observational Studies**

Uveitis in RCT's MEASURE 1-3 (Baeten 2015[95] and Pavelka)[96]

| | Secukin | PBO | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|
| Total uveitis flares | 10 (1.4%) | 2 (0.7%) | Not serious | Not serious | Serious (not all Pts had prior AU) | Serious (low event rate) | Low |
| Subject w/o uveitis | 711 | 269 | | | | | |
| Total subjects | 721 | 271 | | | | | |

Fischer's Exact Test, p=0.53

## Table 2. Observational Data from Indirect Comparisons

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 131, Lie 2017[97] | Observational (Swedish Rheumatology Quality Register) | 2 years | 1365 patients with AS<br>Indirectness: recurrent uveitis not specified; approximately 26% of AS patients with uveitis | TNFi treatment:<br>adalimumab (n=406); etanercept (n=354); infliximab (n=605) | AU rates per 100 patient-years, first 2 years on TNFI vs. 2 years prior to TNFI:<br>Overall AU rates decreased for ADA and IFX vs. pretreatment; AU rates increased for ETN (AU visits total: 13.6 vs. 36.8 ADA, 60.3 vs. 41.6 ETN, 27.5 vs. 45.5 IFX |
| 308, Kim 2016[98] | Retrospective cohort | Mean follow-up 70.6±37.9 months | 143 patients with HLA-B27-positive AS patients; 94 patients with history of uveitis<br>Indirectness: Subset of patients with history of uveitis | ADA (Group 2, n=33) vs. ETN (Group 3, n=19) vs. IFX (Group 1, n=42)<br>Active inflammation at TNFi onset: 13 ADA, 9 ETN, 26 IFX | Uveitis relapse-free survival: no significant difference in patients without uveitis relapse after TNFi (78.8% ADA, 76.2% IFX, 68.4% ETN; p=.692)<br>(Serious adverse effects: tuberculosis was observed in 4 patients (3 IFX, 1 ADA)) |
| 659, Lian 2015[99] | Retrospective observational | minimum 6 mo | 1036 patients with SpA patients (71.6% AS) with active or previous uveitis<br>Indirectness: not all AS patients; only 52% of cases were recurrent uveitis | MTX, SSZ, or TNFi | Monotherapy with adalimumab or infliximab better than etanercept, predominantly for prevention of recurrence.<br>Infliximab and adalimumab associated with more tuberculosis and/or hepatitis flares. |
| 857, Wendling 2014[100] | Retrospective observational | 1 year | 2115 patients with AS naïve to TNFi treatment<br>Indirectness: patients did not have history of uveitis | TNFi therapy with adalimumab (n=717), etanercept (n=1087), or infliximab (n=311) | Incidence of uveitis lowest for patients on adalimumab (2.4%) compared to etanercept (4.5%) and infliximab (3.2%). |
| 1912, Fouache 2009[101] | Retrospective observational | Approx.. 80 mo max | 296 patients with SpA treated with at least one TNFi; 112 comparators treated with DMARDS<br>Indirectness: only 67% AS pts; history of uveitis not specified | TNFi therapy with infliximab, etanercept or adalimumab;<br>DMARDs for control group | Acute anterior uveitis [AAU] cases: TNFi group: n=3 for TNFi group vs. n=3 for controls (n.s.)<br>No significant association among paradoxical adverse events and specific anti-TNF agents. |
| 4213 Cobo-Ibanez[102] | Retrospective observational | 2 yr | 150 patients with SpAs: 15 AS, 2 undifferentiated SpAs; 2 with PsA.<br>Indirectness: Not all AS patients; did not specify patients with recurring uveitis | TNFi therapy with etanercept, infliximab, or adalimumab | Infliximab significantly better than etanercept (p=0.041): uveitis flares decreased with infliximab but increased for etanercept<br>Per-patient rates before/after treatment:<br>infliximab: 0.61+/-0.3 per yr to 0.5 +/- 0.16 (61.73 cases per 100 P-years before to 2.64 after)<br>etanercept: 0.52+/-0.4 per yr to 0.82 +/- 0.99 (34.29 cases per 100 P-years before to 60 after)<br>No observed uveitis flares with adalimumab (drug had only recent approval for SpAs) |
| 2249, Guignard 2006[103] | Retrospective observational | 1.2 years after starting TNFi | 46 patients with SpA, with at least one prior uveitis flare<br>Indirectness: Not all axial SpA; not all pts had recurrent uveitis | TNFi therapy: adalimumab or infliximab | uveitis flares per 100 patient-years before/after anti-TNF:<br>etanercept: 54.6 vs 58.5 (p=0.92)<br>infliximab: 47.4 vs 9.0 (p=0.008)<br>adalimumab: 60.5 vs 0 (p=0.04) |
| 2364, Braun 2005[104] | Pooled analysis: 4 RCTs and 3 open-label studies | Range 6 to 156 weeks | 717 patients with AS who received TNFi treatment<br>Indirectness: Studies specified patients with history of uveitis, not recurrent uveitis | Etanercept, infliximab, or placebo | Flares occurred less frequently (but not significantly less) with infliximab than with etanercept (3.4 per 100 P-years vs. 7.9 per 100 P-years, respectively).<br>AU incidence higher for placebo group (15.6/100 PY) than for TNFi group (6.8/100 PY), $p < 0.01$). |

## PICO 32: In adults with AS and inflammatory bowel disease, is treatment with certain biologics more effective than others in improving outcomes?

*Guidance to voters: At this time, please vote according to the best evidence for TNFi versus secukinumab (non-TNFi biologic). At the last meeting, we voted to compare between TNFi's, however, minimal additional data have been published on that subject since the last guidelines. Keep in mind contraindications that might sway you towards one therapy vs. another (e.g. infection risk). Comparisons between other agents (e.g. sarilumab/tocilizumab, abatacept, ustekinumab, rituximab) will be addressed during the in-person voting meeting by voting on specific pair-wise comparisons.*

Summary: This PICO question was not directly addressed by any study. Very indirect evidence to compare TNFi versus secukinumab may be derived by qualitatively comparing the clinical responses from TNFi RCTs and observational data among AS patients ([Braun, endoscopic data)[105,106], an RCT of etanercept in patients with IBD, and those studies of secukinumab (summarized in Table 1 below from a three RCTs of secukinumab vs. placebo).

The endoscopic study (Chitual 2017)[106] using capsule endoscopy consisted of a prospective observational investigation of subclinical intestinal inflammation in 38 AS patients. Macroscopic intestinal inflammation was defined by a Lewis score of more than 135. Of the 38 AS patients, 16 patients were on a TNFi (5 adalimumab, 5 infliximab, 6 etanercept). Five (31%) of the 16 patients on TNFi also received NSAID. Lewis scores for the whole bowel and distal-, mid- and proximal tertiles of patients taking adalimumab and infliximab were compared with Lewis scores of patients taking etanercept. The Lewis score for distal tertile was statistically significantly better with adaliumumab/infliximab compared with etanercept (Table 1 below).

Indirect evidence to compare among TNFi is also available from a pooled observational study of data from 7 RCTs and 2 open label studies (Braun)[105]. The pooled data study was subsequently revised (with data from an additional study included) in a second report (Gao 2012)[107]. Infliximab was superior to etanercept, and adalimumab was not statistically different from either. The studies demonstrated wide confidence intervals and high risk of bias. This PICO was also indirectly addressed by a single RCT demonstrating the ineffectiveness of etanercept in patients with inflammatory bowel disease without a diagnosis of AS (Sandborn 2001)[108].

Overall quality of evidence for all critical outcomes: Very Low

**Table 1: Summary Evidence on IBD Flares from Secondary Analysis of Observational Studies**

IBD in RCT's MEASURE 1-3 (Baeten 2015 and Pavelka 2017)[95,96]

| | SECUKIN | PBO | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|
| Total Crohn's flares | 4 (0.6%) | 0 (0.0%) | Not serious | Not serious | Serious (not all Ps had IBD) | Serious (low event rate) | Low |
| Subject w/o Crohn's | 717 | 271 | | | | | |
| Total subjects | 721 | 271 | | | | | |

Fischer's Exact Test, p=0.58

## Table 2: ADA/IFX compared to ETN for adults with AS and inflammatory bowel disease

| Table 2: ADA/IFX compared to ETN for adults with AS and inflammatory bowel disease<br>Bibliography: Chitul 2017 [106] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With ETN | With ADA/IFX | | Risk with ETN | Risk difference with ADA/IFX |
| **Lewis score: bowel** | | | | | | | | | | | |
| 16 (1 observational study) | serious [a] | not serious [b] | not serious | serious [c] | none | ⊕◯◯◯ VERY LOW | 6 | 10 | - | - | MD **118 lower** (274.47 lower to 38.47 higher) |
| **Lewis score: distal tertile** | | | | | | | | | | | |
| 16 (1 observational study) | serious [a] | not serious [b] | not serious | serious [d] | none | ⊕◯◯◯ VERY LOW | 6 | 10 | - | - | MD **211 lower** (409.94 lower to 12.06 lower) |
| **Lewis score: proximal tertile** | | | | | | | | | | | |
| 16 (1 observational study) | serious [a] | not serious [b] | not serious | serious [c] | none | ⊕◯◯◯ VERY LOW | 6 | 10 | - | - | MD **30 lower** (154.82 lower to 94.82 higher) |
| **Lewis score: mid tertiles** | | | | | | | | | | | |
| 16 (1 observational study) | serious [a] | not serious [b] | not serious | serious [c] | none | ⊕◯◯◯ VERY LOW | 6 | 10 | - | - | MD **9 lower** (160.59 lower to 142.59 higher) |

**CI:** Confidence interval; **MD:** Mean difference

**Explanations**

a. No randomization, no blinding.
b. Not applicable; single study.
c. Single study. Very wide 95% CI includes the line of no difference.
d. Single study. Very wide 95% CI.

## Table 3. Indirect Evidence (unchanged from 2015 Evidence Report)

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Infliximab | Other TNFs (etanercept) | Relative (95% CI) | Absolute | | |
| **IBD flares (follow-up 14-156 weeks; measured with: IBD flare or onset; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomized trials[1] | very serious[2] | very serious[3] | very serious[4] | very serious[5] | reporting bias[4] | 366 | 419 | - | mean 2 lower (0 to 9 higher) | ⊕OOO VERY LOW | IMPORTANT |

[1] Pooled data from 8 RCTs (1 added later for adalimumab) + 2 open studies.
[2] double blind and open label studies included
[3] Reviewed literature - multiple studies of unknown quality
[4] Some of the rationale is based on scant (small studied) of observed efficacy of these agents in IBD without AS. It's unclear whether this effect translates into outcomes for IBD in the setting of AS.
[5] Post hoc analysis (Gao) published with support from the pharmaceutical company that markets adalimumab substantially changed the result for adalimumab. These revised results suggest adalimumab produced results in between infliximab and etanercept, but was not statistically different from either

## PICO 58: In adults with active AS despite treatment with NSAIDs, is treatment with secukinumab more effective than no treatment with secukinumab in improving outcomes?

*Guidance to voters: At this time, please vote with the assumption that these patients do not have acute uveitis or IBD, as separate PICO questions focus on those clinical scenarios.*

Summary: This PICO question was directly addressed by 4 RCTs reported in three publications. All four trials compared secukinumab versus placebo; one study reporting on two trials administering different secukinumab regimens. We include Deodhar 2016 for BASFI data not available in the primary study (Baeten 2015). Statistically significant differences favoring secukinumab were reported for all efficacy outcomes (including ASAS 20/40/partial remission, BASDAI and BASFI). No statistically significant differences were reported for all safety outcomes; mostly due to very few events being reported.

Overall quality of evidence for all critical outcomes: High

### Table 1. Secukinumab (150 or 300 mg) Versus Placebo for Active AS

**Table 1. Secukinumab (150 or 300 mg) Versus Placebo for Active AS**
**Bibliography: Deodhar 2016[109]; Baeten 2015[95]; Pavelka 2017[96]; Baeten 2013[110]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall certainty of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| | | | | | | | **With placebo, 16 wk** | **With SEC (150 or 300 mg)** | | **Risk with placebo, 16 wk** | **Risk difference with SEC (150 or 300 mg)** |
| ASAS20, 16w | | | | | | | | | | | |
| 724 (4 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 113/354 (31.9%) | 223/370 (60.3%) | **OR 3.24** (2.38 to 4.41) | 319 per 1,000 | **284 more per 1,000** (208 more to 355 more) |
| BASDAI, 16w | | | | | | | | | | | |
| 720 (4 RCTs) | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ HIGH | 351 | 369 | - | - | MD **1.26 lower** (1.66 lower to 0.85 lower) |
| BASFI, 16w | | | | | | | | | | | |
| 247 (1 RCT) | not serious | not serious [a] | not serious | serious [b] | none | ⊕⊕⊕◯ MODERATE | 122 | 125 | - | - | MD **1.4 lower** (1.45 lower to 1.35 lower) |
| Serious AE, 16w | | | | | | | | | | | |
| 920 (4 RCTs) | not serious | not serious | not serious | serious [c] | none | ⊕⊕⊕◯ MODERATE | 10/352 (2.8%) | 15/568 (2.6%) | **OR 0.76** (0.33 to 1.72) | 28 per 1,000 | **7 fewer per 1,000** (19 fewer to 19 more) |
| Death, 16w | | | | | | | | | | | |
| 590 (3 RCTs) | not serious | not serious | not serious | serious [d] | none | ⊕⊕⊕◯ MODERATE | 1/196 (0.5%) | 1/394 (0.3%) | **OR 0.50** (0.05 to 4.84) | 5 per 1,000 | **3 fewer per 1,000** (5 fewer to 19 more) |
| Major adverse cardiac event, adjudicated, 16w | | | | | | | | | | | |
| 590 (2 RCTs) | not serious | not serious | not serious | very serious [d] | none | ⊕⊕◯◯ LOW | 0/196 (0.0%) | 1/394 (0.3%) | **OR 1.55** (0.06 to 38.43) | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

### Explanations

a. Not applicable; single study.
b. Single study; moderate-sized enrollment.
c. Wide 95% CI spans line of no difference.
d. Low event rate; wide 95% CI spanning line of no difference.

**PICO 71: In adults with active non-radiographic axial SpA despite treatment with NSAIDs, is treatment with secukinumab more effective than no treatment with secukinumab in improving outcomes?**

*Guidance to voters: This is similar to PICO 58, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 59: In adults with active AS despite treatment with NSAIDs, is treatment with secukinumab more effective than treatment with TNFi in improving outcomes?

*Guidance to voters: At this time, please vote for with the assumption that these patients do not have acute uveitis or IBD, as separate PICO questions focus on those clinical scenarios. This PICO assesses the preference between agents (focuses on the superiority of secukinumab). At the meeting, we will also vote on the superiority of TNFi.*

Summary: This PICO question was not directly addressed by any study. Indirect evidence to compare TNFi versus secukinumab may be derived by a single meta-analysis described briefly below or by qualitatively comparing the clinical responses among AS patients on TNFi vs. placebo (PICO 6) with those patients on secukinumab vs. placebo (PICO 58).

Though not formally reviewed as evidence for this PICO question, two systematic reviews (Ungprasert 2017; Chen 2016)[13,16] and meta-analyses indirectly compared secukinumab and TNFi. The first did not identify differences in ASAS20 response between secukinumab and older TNFi's (adalimumab, infliximab, etanercept, and golimumab) or between secukinumab and certolizumab pegol, while the findings of the second were less clear. Both meta-analysis did not include a number of published RCTs (Baeten 2013, Pavelka, etc)[96,110], severely hampering comparisons.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 72: In adults with active non-radiographic axial SpA despite treatment with NSAIDs, is treatment with secukinumab more effective than treatment with TNFi in improving outcomes?

*Guidance to voters: This is similar to PICO 59, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 60: In adults with active AS despite treatment with NSAIDs, is treatment with tofacitinib more effective than treatment with TNFi in improving outcomes?

*Guidance to voters: As opposed to PICO 7 (assesses whether you should use tofacitinib or other OSM), this PICO assesses the preference between agents (TNFi vs. tofacitinib).*

Summary: This PICO question was not directly addressed by any study. Very indirect evidence for this PICO may be derived by qualitatively comparing the clinical responses among patients treated with tofacitinib versus placebo (PICO 7) with those patients treated with TNFi vs. placebo (PICO 6).

Though not formally reviewed as evidence for this PICO question, a systematic review (Ungprasert 2017)[16] and meta-analysis indirectly compared tofacitinib and TNFi. This study did not identify differences in ASAS20 response between tofacitinib and older TNFi's (adalimumab, infliximab, etanercept, and golimumab) or between tofacitinib and certolizumab pegol. However, this meta-analysis did not include a number of published RCTs, severely hampering the comparisons.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 73: In adults with active non-radiographic axial SpA despite treatment with NSAIDs, is treatment with tofacitinib more effective than treatment with TNFi in improving outcomes?

*Guidance to voters: This is similar to PICO 60, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 61: In adults with active AS despite treatment with NSAIDs, is treatment with tofacitinib more effective than treatment with secukinumab in improving outcomes?

*Guidance to voters: As opposed to PICO 7 (assesses whether you should use tofacitinib versus placebo) and PICO 58 (secukinumab versus placebo), this PICO assesses the preference between agents (tofacitinib versus secukinumab).*

Summary: This PICO question was not directly addressed by any study. Very indirect evidence for this PICO may be derived by qualitatively comparing the clinical responses among patients treated with tofacitinib versus placebo (PICO 7) with those patients treated with secukinumab versus placebo (PICO 58).

Though not formally reviewed as evidence for this PICO question, a systematic review (Ungprasert 2017)[16] and meta-analysis indirectly compared tofacitinib and secukinumab. This study did not identify differences in ASAS20 response between tofacitinib and secukinumab. However, this meta-analysis did not include a number of published RCTs (Baeten 2013, Pavelka 2017, etc)[96,110], severely hampering comparisons.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 74: In adults with active non-radiographic axial SpA despite treatment with NSAIDs, is treatment with tofacitinib more effective than treatment with secukinumab in improving outcomes?

*Guidance to voters: This is similar to PICO 61, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 62: In adults with active AS despite treatment with the first TNFi agent used, is switching to a different originator TNFi more effective than switching to the first TNFi's biosimilar in improving outcomes?

*Guidance to voters: This PICO does not distinguish between those that never achieved a response (primary failure of TNFi) and those that achieved a clinical response but lost this effect (secondary failures).*

Summary: This PICO question was not directly addressed by any study. Very indirect evidence for this PICO may be derived by qualitatively reviewing the clinical responses among patients who switched TNFi due to active disease (PICO 9). Studies of biosimilars either compared head-to-head with an originator molecule in a naïve population[6-8], or assessed maintenance of disease control in stable patients on an originator switched to a biosimilar for non-medical reasons[111-113]. As such, they are likely not relevant evidence for this PICO.

Though not formally reviewed as evidence for this PICO question, a meta-analysis (Baji 2014)[17] compared the efficacy and safety of infliximab-biosimilar with other biological drugs for the treatment of active AS, however, the subject were not TNFi incomplete responders/failures. No differences could be detected between infliximab-biosimilar versus adalimumab, infliximab originator, etanercept, or golimumab, though confidence intervals were extremely wide.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 75: In adults with active non-radiographic axial SpA despite treatment with the first TNFi agent used, is switching to a different originator TNFi more effective than switching to TNFi biosimilar in improving outcomes?

*Guidance to voters: This is similar to PICO 62, which posed the same question in AS. This PICO does not distinguish between those that never achieved a response (primary failure of TNFi) and those that achieved a clinical response but lost this effect (secondary failures).*

Summary: This PICO question was not directly addressed by any study.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 63: In adults with stable AS on an originator TNFi, is continuation of treatment more effective than switching to its biosimilar TNFi in improving outcomes?

Summary: This PICO question was not directly addressed by any study. This PICO question was indirectly addressed by one RCT (Jorgensen)[111], which reported a sub-stratum analysis for spondyloarthritis (rather than AS) and indirectly by three observational studies[112-114]. In the RCT, stable spondyloarthritis subjects (a "clinical diagnosis of spondyloarthritis"; not further defined) were randomized to infliximab originator molecule, or an infliximab biosimilar. Results at 52 weeks did not differ for ASDAS, ASDAS-inactivity, and BASDAI between the two therapeutic agents.
The observational studies were limited by indirectness and disease activity that was only "borderline" stable (Benucci 2017), as well as a lack of comparator groups.

Overall quality of evidence for all critical outcomes: Very Low

### Table 1. Continued Infliximab vs Switch to CT-P13 for stable AS

**Table 1. Continued Infliximab vs Switch to CT-P13 for stable AS**
**Bibliography: Jorgensen 2017[111]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall certainty of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| | | | | | | | **With swtich to CT-P13, 52 wk** | **With continue Infliximab** | | **Risk with swtich to CT-P13, 52 wk** | **Risk difference with continue Infliximab** |
| change in ASDAS, 52w | | | | | | | | | | | |
| 408 (1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⨁⨁◯◯ LOW | 202 | 206 | - | - | MD **0.3 lower** (0.43 lower to 0.17 lower) |
| ASDAS inactive disease, 52w | | | | | | | | | | | |
| 408 (1 RCT) | not serious | not serious [a] | serious [b] | serious [d] | none | ⨁⨁◯◯ LOW | 10/202 (5.0%) | 7/206 (3.4%) | **OR 0.68** (0.25 to 1.81) | 50 per 1,000 | **15 fewer per 1,000** (37 fewer to 37 more) |
| change in BASDAI, 52w | | | | | | | | | | | |
| 408 (1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⨁⨁◯◯ LOW | 202 | 206 | - | - | MD **0.5 lower** (0.74 lower to 0.26 lower) |

**CI:** Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

### Explanations

a. Not applicable; single study.
b. Does not specify axial SpA.
c. Single study; small enrollment of axial SpA patients.
d. Single study; wide 95% CI that spans line of no difference.

**Table 2. Observational Data on Switch from Inflixmab to CT-P13 (all indirect evidence)**

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 317, Benucci 2017[114] | Observational study | 6 mo | 41 patients with previous diagnosis of SpA and clinically inactive or moderate disease activity | Switch from originator infliximab to biosimilar infliximab (following > 6 months treatment)<br><br>Indirectness: no direct comparison to continuation on INX; single-arm study; 54% patients with AS | base / 6 mo. post-switch<br>BASDAI 2.73 ± 1.5 / 2.6 ± 1.3 (p=0.27)<br>BASFI 2.34 ± 1.3 / 2.17 ± 1.2 (p=0.051)<br>ASDAS-CRP 1.35 ± 0.3 / 1.28 ± 0.2 (p=0.92)<br>MASES 0.35 ± 0.7 / 0.17 ± 0.4 (p=0.08)<br>VAS pain 18 ± 14.7 / 16.7 ± 11.3 (p=0.55)<br>Morning stiffness 7.2 ± 6.9 / 5.8 ± 6 (*p=0.02)<br><br>Very few patients experienced an AE with biosimilar infliximab, and there was no significance difference from the AEs recorded prior to the medication switch (p=1.0). |
| 95, Glintborg 2017[112] | Observational before/after Danish registry study | 1 yr | 279 patients with Axial SpA (802 patients overall) | Non-medical switch from infliximab to biosimilar CT-P13; switch dictated by change to national guideline<br><br>Indirectness: no direct comparison to continuation on INX | BASDAI: No significant difference in pre-switch vs. post-switch changes (0.0 [95%CI -4 to 5] vs. 0.0 [-4.0 to 7.0]; p=0.3)<br>raw scores: 2.0 (1.4 to 2.6) at switch; 2.0 (1.2 to 2.9) at 3 months post-switch<br><br>ASDAS: No significant difference in pre-switch vs. post-switch changes (0.0 [95%CI -0.3 to 0.4] vs. 0.0 [-0.3 to 0.3]; p=0.8)<br>Raw scores: 2.0 (1.4 to 2.6) at switch; 2.0 (1.2 to 2.9) at 3 months post-switch |
| 519, Nikiphorou 2015[113] | Prospective observational study | Median 11 mo (range 7.5-13) | 39 consecutive patients with various rheumatic disease | Infliximab (INX) treatment (mean 4.1 ± 2.3 yrs) followed by switch to CT-P13<br><br>Majority patients on concomitant MTX (79%) or other DMARDs<br><br>Indirectness: only 36% AS patients; no direct comparison to INX | Pain: 26 with INX vs. 24 with CT-P13, p=0.36<br><br>Patient Global Estimate: 26 with INX vs. 24 with CT-P13, p=0.24<br><br>HAQ: 0.58 with INX vs. 0.61 with CT-P13, p=0.44 |

## PICO 76: In adults with stable non-radiographic axial SpA on an originator TNFi, is continuation of treatment more effective than switching to its biosimilar TNFi in improving outcomes?

*Guidance to voters: This is similar to PICO 63, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 64: In adults with either active or stable AS on treatment with TNFi, is co-treatment with low-dose methotrexate more effective than no co-treatment with low-dose methotrexate in improving outcomes?

*Guidance to voters: If your vote is different for active and stable disease, vote only for active and we will adjust the PICO next time. Please note this in your comments.*

Summary: This PICO question was directly addressed by two small RCTs (Mulleman 2011 and Li 2008)[115,116] and one observational study (Nissen 2016)[117], which reported clinical outcomes. This PICO question was indirectly addressed by one RCT (Breban 2008)[118], a prospective open-label interventional study (Perez-Guijo 2007)[119] and 13 observational studies. The most direct evidence from the Mulleman (republished with additional data as Ternant et al Br J Clin Pharm 2012;73:55-65) and Li et al. RCTs found combination treatment with MTX and infliximab to have similar efficacy and safety as infliximab monotherapy.

The indirect evidence from the RCT (Breban 2008)[118] was presented in the subset of patients randomized to the on-demand (non-continuous) infliximab treatment arm, who were further randomized to receive methotrexate in conjunction with infliximab or infliximab alone (with no methotrexate). On-demand treatment with infliximab was given only upon symptom recurrence (relapse) with a minimum interval of 4 weeks between infusions (following an initial loading regimen) while methotrexate dose was limited to 12.5 mg. At 58 weeks, the addition of methotrexate to infliximab had no significant effect on major outcomes compared with on-demand infliximab. The low strength of evidence for outcomes were attributed to limited data from a single study with a small patient population (imprecision) and indirectness of the comparison, due to infliximab being provided on an as-needed basis rather than continuously.

Perez-Guijo was a small, prospective open label observation study of 19 patients with active AS who had an incomplete prior response to NSAIDs, methotrexate (MTX), and sulfasalazine. Two group of patients were treated with IFX and MTX (n=9) or IFX alone (n=10), however, patient assignments were based on previous treatments; patients previously treated with MTX had IFX added to their regimen while those treated only with NSAIDs were treated with IFX alone. The found that MTX in combination with infliximab increased efficacy of therapeutic response.

Of the 13 remaining observational studies (Nissen 2016; Glintborg 2010; Heiberg 2008; Kristensen 2010; Favalli 2017; Rahman 2016; Heinonen 2015; Lie 2015; Sepriano 2016; Scire 2013)[117,120-128] with indirect evidence, nine assessed persistence of drug regimen (drug discontinuation) among those on co-treatment vs. without co-treatment) or evaluated for the presence of anti-drug antibodies (four studies; most compared antibodies among those on co-treatment vs. without co-treatment) (de Vries 2009; de Vries 2007; de Vries 2007; Kneepkens 2015)[129-132]. Among all these studies, clinical outcomes were not reported (they were reported only in Nissen, et al AR 2016; 68:2141-50, as described above, though results were not stratified by MTX or SSZ). In the Nissen study, no difference in BASDAI (mean decrease 2.0 in both groups) or ASDAS (mean decrease 1.1 in both groups) at 1 year was evident in patients on MTX or SSZ versus those not taking co-treatment. Half of the studies (5 out of the 10, which included Nissen and 9 other studies) showed greater persistence/lower drug discontinuation with co-treatment, particularly for the combination of infliximab and methotrexate. Some of the four studies of anti-drug antibodies did include clinical outcomes, however, they compared results of those with antibodies versus those without antibodies, rather than outcomes for patients receiving co-treatment or no co-treatment. One study of infliximab and two with adalimumab showed lower response in the presence of anti-drug antibodies, however, no anti-drug antibodies were identified in a fourth study with etanercept.

Overall quality of evidence for all critical outcomes: Low

## Table 1: Infliximab with MTX compared to Infliximab alone for patients with active AS, 18 or 30w (randomized trials; direct evidence)

| Table 1: Infliximab with MTX compared to Infliximab alone for patients with active AS, 18 or 30w (randomized trials; direct evidence)<br>Bibliography: Mulleman 2011; Li 2008 [115,116] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With infliximab alone, 18 or 30 wks | With Infliximab with MTX | | Risk with infliximab alone, 18 or 30 wks | Risk difference with Infliximab with MTX |
| **ASAS20 response, 18 or 30w** | | | | | | | | | | | |
| 64 (2 RCTs) | not serious | not serious | not serious | serious [a] | none | ⊕⊕⊕◯ MODERATE | 20/31 (64.5%) | 22/33 (66.7%) | **OR 1.10** (0.39 to 3.07) | 645 per 1,000 | **22 more per 1,000** (230 fewer to 203 more) |
| **ASAS40 response, 30w** | | | | | | | | | | | |
| 38 (1 RCT) | not serious | not serious [b] | not serious | serious [c] | none | ⊕⊕⊕◯ MODERATE | 5/19 (26.3%) | 5/19 (26.3%) | **OR 1.00** (0.24 to 4.24) | 263 per 1,000 | **0 fewer per 1,000** (184 fewer to 339 more) |
| **BASDAI response, 18w** | | | | | | | | | | | |
| 28 (1 RCT) | serious [d] | not serious [b] | not serious | serious [c] | none | ⊕⊕◯◯ LOW | 7/14 (50.0%) | 8/14 (57.1%) | **OR 1.33** (0.30 to 5.91) | 500 per 1,000 | **71 more per 1,000** (269 fewer to 355 more) |
| **Partial remission, 30w** | | | | | | | | | | | |
| 38 (1 RCT) | not serious | not serious [b] | not serious | serious [c] | none | ⊕⊕⊕◯ MODERATE | 15/19 (78.9%) | 15/19 (78.9%) | **OR 1.00** (0.21 to 4.76) | 789 per 1,000 | **0 fewer per 1,000** (349 fewer to 157 more) |
| **Overall adverse events, 30w** | | | | | | | | | | | |
| 38 (1 RCT) | not serious | not serious [b] | not serious | serious [c] | none | ⊕⊕⊕◯ MODERATE | 13/19 (68.4%) | 15/19 (78.9%) | **OR 1.73** (0.40 to 7.51) | 684 per 1,000 | **105 more per 1,000** (220 fewer to 258 more) |

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

### Explanations

a. Wide 95% CI spans line of no difference.
b. Not applicable; single study.
c. Single study; small enrollment. Wide 95% CI.
d. Unblinded trial.

## Table 2: Infliximab with methotrexate compared to Infliximab alone for patients with active AS, 30w (observational study; indirect evidence)

| Table 2: Infliximab with methotrexate compared to Infliximab alone for patients with active AS, 30w (observational study; indirect evidence)<br>Bibliography: Perez-Guijo 2007 [119] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With Infliximab alone, 30 wks (observational study) | With Infliximab with MTX | | Risk with Infliximab alone, 30 wks (observational study) | Risk difference with Infliximab with MTX |
| **BASDAI 50, 30w** | | | | | | | | | | | |
| 19 (1 observational study) | serious [a] | not serious [b] | not serious | serious [c] | none | ⊕◯◯◯ VERY LOW | 1/10 (10.0%) | 8/9 (88.9%) | **OR 72.00** (3.84 to 1349.55) | 100 per 1,000 | **789 more per 1,000** (199 more to 893 more) |
| **ASAS 20, 30w** | | | | | | | | | | | |
| 19 (1 observational study) | serious [a] | not serious [b] | not serious | serious [c] | none | ⊕◯◯◯ VERY LOW | 2/10 (20.0%) | 8/9 (88.9%) | **OR 32.00** (2.39 to 427.74) | 200 per 1,000 | **689 more per 1,000** (174 more to 791 more) |
| **ASAS 50, 30w** | | | | | | | | | | | |

| Table 2: Infliximab with methotrexate compared to Infliximab alone for patients with active AS, 30w (observational study; indirect evidence)<br>Bibliography: Perez-Guijo 2007 [119] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| 19<br>(1 observational study) | serious [a] | not serious [b] | not serious | serious [c] | none | ⊕◯◯◯<br>VERY LOW | 0/10 (0.0%) | 5/9<br>(55.6%) | **OR 25.67**<br>(1.16 to 568.91) | 0 per 1,000 | **0 fewer per 1,000**<br>(0 fewer to 0 fewer) |
| **Partial remission, 30w** | | | | | | | | | | | |
| 19<br>(1 observational study) | serious [a] | not serious [b] | not serious | serious [d] | none | ⊕◯◯◯<br>VERY LOW | 0/10 (0.0%) | 3/9<br>(33.3%) | **OR 11.31**<br>(0.50 to 256.20) | 0 per 1,000 | **0 fewer per 1,000**<br>(0 fewer to 0 fewer) |

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

## Explanations

a. Observational study.
b. Not applicable; single study.
c. Single study; very small enrollment. Very wide 95% CI.
d. Single study; very small enrollment. Very wide 95% CI includes line of no difference.

## Table 3: Infliximab with methotrexate vs. infliximab alone for treatment of adult patients with active or stable AS (indirect evidence)

| Table 3: Infliximab with methotrexate vs. infliximab alone for treatment of adult patients with active or stable AS (indirect evidence)<br>Bibliography: Breban 2008 [118] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall certainty of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| | | | | | | | **With no Co-treatment, 58 wks** | **With Co-treatment with MDX** | | **Risk with no Co-treatment, 58 wks** | **Risk difference with Co-treatment with MDX** |
| **ASAS20 response (58w)** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 25/62<br>(40.3%) | 31/61<br>(50.8%) | **OR 1.53**<br>(0.75 to 3.12) | 403 per 1,000 | **105 more per 1,000**<br>(67 fewer to 275 more) |
| **ASAS40 response, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 15/62<br>(24.2%) | 22/61<br>(36.1%) | **OR 1.77**<br>(0.81 to 3.86) | 242 per 1,000 | **119 more per 1,000**<br>(37 fewer to 310 more) |
| **Partial remission, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,e] | none | ⊕⊕◯◯<br>LOW | 3/62 (4.8%) | 6/61 (9.8%) | **OR 2.15**<br>(0.51 to 9.00) | 48 per 1,000 | **50 more per 1,000**<br>(23 fewer to 266 more) |
| **Assessment of pain (0-10 scale), 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 62 | 61 | - | - | MD **0.3 lower**<br>(1.24 lower to 0.64 higher) |
| **Change in patient global assessment (0-10 scale), 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 62 | 61 | - | - | MD **0.8 lower**<br>(1.68 lower to 0.08 higher) |
| **BASDAI (change), 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 62 | 61 | - | - | MD **0.2 higher**<br>(0.49 lower to 0.89 higher) |
| **BASFI change, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 62 | 61 | - | - | MD **0.5 lower**<br>(1.19 lower to 0.19 higher) |
| **SF-36 Physical component, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 62 | 61 | - | - | MD **0.1 lower**<br>(2.98 lower to 2.78 higher) |
| **Schober test, cm, 58w** | | | | | | | | | | | |

| Table 3: Infliximab with methotrexate vs. infliximab alone for treatment of adult patients with active or stable AS (indirect evidence)<br>Bibliography: Breban 2008 [118] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 62 | 61 | - | - | MD **0.1 higher**<br>(0.43 lower to 0.63 higher) |
| **Fingers to floor distance, cm, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,e] | none | ⊕⊕◯◯<br>LOW | 61 | 62 | - | - | MD **2.6 higher**<br>(2.51 lower to 7.71 higher) |
| **Occiput to wall distance, cm, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 62 | 61 | - | - | MD **0.3 lower**<br>(1.87 lower to 1.27 higher) |
| **Chest expansion, cm, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,d] | none | ⊕⊕◯◯<br>LOW | 62 | 61 | - | - | MD **0**<br>(0.6 lower to 0.6 higher) |
| **Death, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,e,f] | none | ⊕⊕◯◯<br>LOW | 0/62 (0.0%) | 1/61 (1.6%) | **OR 3.10**<br>(0.12 to 77.57) | 0 per 1,000 | **0 fewer per 1,000**<br>(0 fewer to 0 fewer) |
| **Cancer, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,e,f] | none | ⊕⊕◯◯<br>LOW | 0/62 (0.0%) | 1/61 (1.6%) | **OR 3.10**<br>(0.12 to 77.57) | 0 per 1,000 | **0 fewer per 1,000**<br>(0 fewer to 0 fewer) |
| **Serious infection, 58w** | | | | | | | | | | | |
| 123<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c,e] | none | ⊕⊕◯◯<br>LOW | 1/62 (1.6%) | 3/61 (4.9%) | **OR 3.16**<br>(0.32 to 31.21) | 16 per 1,000 | **33 more per 1,000**<br>(11 fewer to 322 more) |

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

## Explanations

a. Not applicable; single study
b. Indirect comparison: infliximab treatment on as-needed basis.
c. Single study, small enrollment
d. 95% CI includes possibility of no difference
e. Wide 95% CI includes possibility of no difference.
f. Event with very low incidence of occurrence.

## PICO 77: In adults with either active or stable non-radiographic axial SpA on treatment with TNFi, is co-treatment with low-dose methotrexate more effective than no co-treatment with low-dose methotrexate in improving outcomes?

*Guidance to voters: This is similar to PICO 64, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study. Indirect evidence for this PICO may be derived from a single observational study (Gulfe 2014)[133] that examined the efficacy and medication persistence of TNFi in nr-axSpA. In this study of 119 individuals, "concomitant non-biological DMARD use" was not associated with medication persistence. Results were not reported separately for methotrexate nor were efficacy outcomes compared between those on methotrexate and those without.

Overall quality of evidence for all critical outcomes: Low

### Table 1. Observational Data (indirect evidence)

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 873, Gulfe 2014[133] | Prospective observational | 6 months | 112 patients with nr-axSpA and high disease activity<br><br>(Inadequate response or intolerance to non-steroidal anti-inflammatory drugs (NSAIDs) and first course of TNFi treatment)<br><br>Median disease duration was 6 years and 10 months | TNFi therapy<br><br>recommended doses used , except infliximab (infusion of 3 mg/kg at 0, 2, 6, and then every 8 weeks)<br><br>Indirectness: 38% patients on DMARD use prior to TNFi therapy | median BASDAI: decrease from 5.6 to 3.2 (p=0.002)<br>median BASFI: decrease from 3.9 to 1.8 (p=0.005)<br>C-reactive protein (CRP) level: decreased from 4.4 to 1.7 mg/L (p = 0.001)<br>Kaplan–Meier-estimated drug survival at 2 years of follow-up was 65% |

## PICO 65: In adults with stable AS on treatment with a biologic, is tapering of the biologic dose more effective than no tapering in improving outcomes?

*Guidance to voters: This PICO focuses on dose reduction (either by decreasing the frequency of administration or the dose administered). It does not address discontinuation of the biologic.*

Summary: This PICO question was directly addressed by 2 RCTs (Yates 2015, Cantini 2013)[134,135]. This PICO question was indirectly addressed by one RCT (Li 2016)[136], which examined tapering in a population that was fairly active (all with synovitis of the hip). A number of observational studies also provided indirect evidence based on prospective study designs (Arends 2015; Lee 2008; DeStefano 2014; Almirall 2015)[137-140] and retrospective study designs (Plasencia 2015, Navarro-Compan, Zavada as well as Lee 2010 ; Paccou 2012; Fong 2016, Park 2016; Morck 2013, Chen 2018)[141-149] These studies were generally small (n<50) and the Plasencia study was comprised of only 74% AS patients).

The first RCT (Cantini 2013)[135] included patients who had achieved remission with use of etanercept and randomized them to continued weekly 50 mg dose treatment (n=21) or to bi-weekly treatment with the same dose (n=22) (see Table 1 below). The second RCT (Yates 2015)[134] randomized patients who responded to 6 months of etanercept 50 mg/wk to either continue this dose of etanercept or taper to 25mg/wk (Table 2). These two studies demonstrated that approximately 90% and 50% (respectively) of the cohorts that tapered their TNFi from these studies maintained their remission. The RCT by Li et al. reported that both the standard and dose-reduction groups of active AS patients showed statistically-significant decreases in BASDAI scores, but there was no significant difference in this trend between the two groups (see Table 3). The study was indirect evidence because patients were active.

Overall, results from the observational studies suggest that switches to tapered treatment regimens with biologics for patients with stable disease has no significant effect on most major outcomes. Approximately 50-90% of subjects remained in clinical remission at 1 year after decreasing the frequency or dose by one half.

Overall quality of evidence across all critical outcomes: Very low to Low

## Table 1: Standard vs. Tapered treatment with TNFi (etanercept): long-term F/U for improving outcomes in adults with stable AS (direct evidence)

| Table 1: Standard vs. Tapered treatment with TNFi (etanercept): long-term F/U for improving outcomes in adults with stable AS (direct evidence)<br>Bibliography: Cantini 2013 [135] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Certainty assessment** | | | | | | | **Summary of findings** | | | | |
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall certainty of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| | | | | | | | **With tapered treatment** | **With TNFi Standard** | | **Risk with tapered treatment** | **Risk difference with TNFi Standard** |
| **Time until disease relapse** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁⨁◯◯ LOW | 21 | 22 | - | - | MD **2 lower** (3.42 lower to 0.58 lower) |
| **Relapse** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [d] | none | ⨁⨁◯◯ LOW | 2/21 (9.5%) | 3/22 (13.6%) | **OR 1.50** (0.22 to 10.02) | 95 per 1,000 | **41 more per 1,000** (73 fewer to 418 more) |
| **Remission** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [d] | none | ⨁⨁◯◯ LOW | 19/21 (90.5%) | 19/22 (86.4%) | **OR 0.67** (0.10 to 4.45) | 905 per 1,000 | **41 fewer per 1,000** (418 fewer to 72 more) |
| **mean change BASDAI, 2 yr** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁⨁◯◯ LOW | 21 | 22 | - | - | MD **0.1 higher** (0.31 lower to 0.51 higher) |
| **mean change BASFI, 2 yr** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁⨁◯◯ LOW | 21 | 22 | - | - | MD **0** (0.71 lower to 0.71 higher) |
| **change in BASMI, 2 yr** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁⨁◯◯ LOW | 21 | 22 | - | - | MD **0.1 higher** (0.56 lower to 0.76 higher) |
| **Modified Schober test, 2 yr** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁⨁◯◯ LOW | 21 | 22 | - | - | MD **0.2 higher** (0.86 lower to 1.26 higher) |
| **Fingertip to floor distance, 2 yr** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁⨁◯◯ LOW | 21 | 22 | - | - | MD **0.1 higher** (1.38 lower to 1.58 higher) |
| **Chest expansion, 2 yr** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁⨁◯◯ LOW | 21 | 22 | - | - | MD **0** (0.31 lower to 0.31 higher) |
| **Urinary infections, 2 yr** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [d] | none | ⨁⨁◯◯ LOW | 1/21 (4.8%) | 2/22 (9.1%) | **OR 2.00** (0.17 to 23.86) | 48 per 1,000 | **43 more per 1,000** (39 fewer to 496 more) |
| **Upper airway infections, 2 yr** | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [d] | none | ⨁⨁◯◯ LOW | 5/21 (23.8%) | 7/22 (31.8%) | **OR 1.49** (0.39 to 5.74) | 238 per 1,000 | **80 more per 1,000** (129 fewer to 404 more) |

**CI:** Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

### Explanations

a. Unblinded study. Most methodologies not clearly explained.
b. Not applicable; single study.
c. Results from a single study with small enrollment.
d. Single study. Very wide 95% CI includes possibility of no difference.
e. Single study. 95% CI includes possibility of no difference.
f. Very low event rate; very wide CI includes possibility of no difference.

## Table 2. ETN 50 mg/wk compared to 25 mg/wk, 6 mo for adults with stable AS (direct evidence)

| Table 2. ETN 50 mg/wk compared to 25 mg/wk, 6 mo for adults with stable AS (direct evidence)<br>Bibliography: Yates 2015 [134] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With 25 mg/wk, 6 mo | With ETN 50 mg/wk | | Risk with 25 mg/wk, 6 mo | Risk difference with ETN 50 mg/wk |
| **ASAS20, 6 mo** | | | | | | | | | | | |
| 47 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁⨁◯◯ LOW | 20/24 (83.3%) | 14/23 (60.9%) | **OR 0.31** (0.08 to 1.21) | 833 per 1,000 | **225 fewer per 1,000** (548 fewer to 25 more) |
| **ASAS partial remission, 6 mo** | | | | | | | | | | | |
| 47 (1 RCT) | serious [a] | not serious [b] | not serious | serious [d] | none | ⨁⨁◯◯ LOW | 7/24 (29.2%) | 1/23 (4.3%) | **OR 0.11** (0.01 to 0.99) | 292 per 1,000 | **248 fewer per 1,000** (288 fewer to 2 fewer) |
| **BASDAI50, 6 mo** | | | | | | | | | | | |
| 47 (1 RCT) | serious [a] | not serious [b] | not serious | serious [d] | none | ⨁⨁◯◯ LOW | 16/24 (66.7%) | 8/23 (34.8%) | **OR 0.27** (0.08 to 0.89) | 667 per 1,000 | **316 fewer per 1,000** (529 fewer to 26 fewer) |
| **Complete clinical response, 6 mo** | | | | | | | | | | | |
| 47 (1 RCT) | serious [a] | not serious [b] | not serious | serious [d] | none | ⨁⨁◯◯ LOW | 20/24 (83.3%) | 12/23 (52.2%) | **OR 0.22** (0.06 to 0.84) | 833 per 1,000 | **310 fewer per 1,000** (603 fewer to 26 fewer) |
| **Change in CRP (mg/l), 6 mo** | | | | | | | | | | | |
| 47 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁⨁◯◯ LOW | 24 | 23 | - | - | MD **0.2 lower** (0.78 lower to 0.39 higher) |
| **Serious adverse events, 6 mo** | | | | | | | | | | | |
| 47 (1 RCT) | serious [a] | not serious [b] | not serious | serious [e] | none | ⨁⨁◯◯ LOW | 0/24 (0.0%) | 0/23 (0.0%) | not estimable | 0 per 1,000 | **Not estimable** |

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

## Explanations

a. Unblinded study.
b. Not applicable; single study.
c. Single study; small enrollment. 95% CI spans line of no difference.
d. Single study; small enrollment.
e. No events recorded.

## Table 3: TNFi Standard compared to tapered treatment: long-term F/U for improving outcomes in adults with stable AS (indirect evidence)

**Table 3: TNFi Standard compared to tapered treatment: long-term FU for improving outcomes in adults with stable AS (indirect evidence)**
**Bibliography: Plasencia 2015; Zavada 2016 [141,142]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall certainty of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| | | | | | | | **With tapered treatment: long-term FU** | **With TNFi Standard** | | **Risk with tapered treatment: long-term FU** | **Risk difference with TNFi Standard** |
| **mean change BASDAI, 2 yr** | | | | | | | | | | | |
| 253 (2 observational studies) | serious [a] | not serious | not serious | not serious | none | ⨁◯◯◯ VERY LOW | 126 | 127 | - | - | MD **0.03 higher** (0.22 lower to 0.28 higher) |
| **mean change BASFI, 2 yr** | | | | | | | | | | | |
| 136 (1 observational study) | serious [a] | not serious [b] | not serious | not serious | none | ⨁◯◯◯ VERY LOW | 83 | 53 | - | - | MD **0.02 higher** (0.4 lower to 0.44 higher) |
| **Disease flares** | | | | | | | | | | | |
| 117 (1 observational study) | serious [a] | not serious [b] | not serious | serious [c] | none | ⨁◯◯◯ VERY LOW | 8/43 (18.6%) | 22/74 (29.7%) | **OR 1.85** (0.74 to 4.62) | 186 per 1,000 | **111 more per 1,000** (41 fewer to 328 more) |

**CI:** Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

### Explanations

a. One of 2 observational studies was retrospective.
b. Not applicable; single study.
c. Wide 95%CI includes line of no difference.

## Table 4: Etanercept (50 mg) Every Other Week vs. Weekly for Adults with Active AS (indirect evidence)

**Table 4: Etanercept (50 mg) Every Other Week vs. Weekly for Adults with Active AS (indirect evidence)**
**Bibliography: Li 2016 [136]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall certainty of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| | | | | | | | **With weekly: short-term FU** | **With ETN (50 mg) every other week** | | **Risk with weekly: short-term FU** | **Risk difference with ETN (50 mg) every other week** |
| Mean change BASDAI score, 12 weeks | | | | | | | | | | | |
| 43 (1 RCT) | serious [a] | not serious [b] | not serious | serious [c] | none | ⊕⊕◯◯ LOW | 17 | 26 | - | - | MD **0.32 lower** (0.69 lower to 0.05 higher) |

**CI:** Confidence interval; **MD:** Mean difference

### Explanations

a. Unblinded study. Methodological details lacking.
b. Not applicable; single study.
c. Single study; very limited enrollment.

## Table 5. Additional Observational Data (indirect evidence)

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 4087, Chen 2018[149] | Observational | 1 yr | N=450 patients (120 with AS; 330 with RA) | Reduction or discontinuation of biological DMARD therapy (adalimumab, etanercept, golimumab, tocilizumab, abatacept, and rituximab)<br>Indirectness: No direct comparison of taper to non-tapered treatment. | SF-36 and Global Quality of Life (GQL): Reduction or discontinuation of DMARDs resulted in significant decreases in all domains of the SF-36 and GQL in both AS and RA groups.<br><br>Relapse rate: 50% for AS patients; 90% for RA patients |
| 446, Almirall 2016[140] | Observational | Mean 42 months (±18.8 mo) | N=20 patients with axial SpA who remained in low disease activity > 1 yr after tapering infliximab or adalimumab | lowering the dose of infliximab to 3 mg/kg every 8 weeks;<br>extending inter-dose interval of adalimumab to 40 mg every 3 weeks<br>Indirectness: No direct comparison of taper to non-tapered treatment. | Data could support tapering of biological drugs in patients with low disease activity.<br><br>18 of 20 had therapeutic drug levels,<br>no patients had anti-drug antibodies<br>no patients had active sacroiliitis on MRI |
| 346, Fong 2011[146] | Retrospective observational | 24 weeks | N=48 patients with AS (n=33) or PsA (n=15) who reached stable disease on TNFi therapy | TNFi dose reduction by approx. one-third; dose was reduced or interval between doses extended<br>TNFis used were adalimumab, etanercept, infliximab, or certiluzimab<br>Indirectness: No direct comparison of taper to non-tapered treatment. | Approx. 60% of patients with severe AS or PsA who achieve low disease activity can reduce TNFi dose by one-third for a mean of 1 year.<br>Disease activity at 24 weeks similar in AS patients who had dose reduced compared with patients who were eligible but did not have their TNFi reduced: BASDAI 2.3 ± 1.8 vs 2.4 ± 1.0, respectively (p = 0.811).<br>19 of 33 (58%) AS and 9 of 15 (60%) PsA patients maintained TNFi dose reduction for average of 1.0 ± 0.8 years. Reinstating standard TNFi dose recaptured low disease activity in all patients who failed dose reduction. |
| 2824, Li 2016[136] | Randomized comparison study | 12 weeks | 43 patients with AS | Etanercept at conventional dosing (n=17) vs. dose reduction regimen (n=26) | Change in BASDAI: Scores decreased significantly over 12 weeks in both groups (p<0.001): from 4.82 ± 0.69 to 1.42 ± 0.23 for dose reduction group vs. 5.12 ± 0.68 to 1.40 ± 0.35 for conventional treatment group (n.s. difference between groups) |

| | | | | | |
|---|---|---|---|---|---|
| Add'l data not in RevMan | | | | Indirectness: Limited to AS patients with synovitis of the hip (so pts had active disease at baseline). | Adverse events: No serious adverse events or events leading to withdrawal in either group. |
| 178, Park 2016[147] | Retrospective cohort study | 2 yr | 165 patients with AS | Etanercept or adalimumab<br>Standard dose (n=49) vs. tapered dose (n=116)<br>Indirectness: Tapering dose customized across pts at physician discretion. Restricted enrollment to patients with cervical and lumbar radiographs. | Baseline characteristics between two groups comparable except for higher BASDAI for standard dose group (7.1 vs. 6.3, p = 0.003).<br><br>mSASSS progression: similar for standard and tapered dose groups; the subgroup of patients with baseline syndesmophytes progressed significantly faster in the tapering group after the adjustment for baseline status (1.23 vs. 1.72 mSASSS units/year, p = 0.023). |
| 721, Arends 2015[137] | Observational follow-up | 24 months | 58 patients with AS | Pts-tailored dose reduction of etanercept (n=39), infliximab (n=10), or adalimumab (n=9)<br>Indirectness: No direct comparison of taper to non-tapered treatment. Dose reductions were at physicians' discretion. | 74%, 62%, and 53% maintained reduced dose or dosing frequency after 6, 12, and 24 months, respectively<br><br>94% patients had BASDAI < 4 after maintaining dose reduction for 24 months |
| 1120, De Stefano 2014[139] | Prospective cohort | 48 weeks | N=21 patients who reached partial remission on 50 mg/wk etanercept (ETN) | Reduction of ETN dose from 25 mg, 2x/wk (12w) to 1x/wk<br>Indirectness: No direct comparison of taper to non-tapered treatment. | 24 weeks: 20 of 21 patients (95.2%) remained in remission at reduced dose<br><br>36 weeks: 16 of original 21 patients (76.2%) in remission at 24 weeks remained in remission at reduced dose<br><br>48 weeks: 16 of original 21 patients (76.2%) in remission at 24 weeks remained in remission at reduced dose |
| 1113, Morck 2013[148] | Prospective observational | 2 yr | N=18 patients completing 56 weeks of treatment with IFX | Dose reduction and interval extension of IFX<br>Reduced to 3 mg/kg every 8 wks after 5 mg/kg every 6 wks<br>Indirectness: No direct comparison of taper to non-tapered treatment. | BASDAI: No significant increase in BASDAI median 2.1 (IQR 0.6 to 3.6) vs. 3.2 (0.4 to 4.2) after dose reduction, n.s.<br>CRP (mg/L): median 8 (IQR 8 to 8) vs. 8 (5 to 8) after dose reduction, n.s. |
| 1389, Paccou 2012[145] | Retro observational | Mean 43.5 months (±17.9) | N=65 patients with AS who achieved remission | Dose reduction of adalimumab, etanercept, or infliximab<br>Indirectness: No direct comparison of taper to non-tapered treatment. | Dosage adjustment and reduction of treatment frequency was effective in maintaining remission.<br>6-month follow-up after dose adjustment:<br>ADA: remission maintained in 5 of 5 patients (100%)<br>ETN: remission maintained in 12 of 17 patients (70.6%)<br>IFX: remission maintained in 26 of 27 patients (96.3%)<br><br>Cumulative probability of continuing TNFi after dosage adjustment was 79.0% at 12 months, 70.5% at 24 months, and 58.8% at 36 months. |
| 1626 Navarro-Compan 2011[143] | Case series | Mean 26.1 months | 16 patients switched to low-dose etanercept | Dose reduction with etanercept (from 50 mg/week) to lower dose, variable across patients.<br>Indirectness: No direct comparison of taper to non-tapered treatment. | Median scores and (ranges) at starting the low-dose regimen and 6 months later, respectively:<br>BASDAI: 1.6 (0.9 to 2.4) and 1.4 (0.3 to 3.2)<br>BASFI: 2.2 (0.8 to 3.9) and 2.5 (0.8 to 3.2)<br>Patient global assessment: 15 (10 to 30) and 10 (2.5 to 20)<br><br>Patients with follow-up at 12 months (n=12), 24 months (n=7), or longer (n=5) remained in clinical remission with BASDAI values <2 and normal CRP values (<5 mg/L). No serious adverse events were reported during the study. |
| 2127, Lee 2008[138] | Prospective observational study | 6 mo | N=18 patients with active AS who reached remission on 50 mg/wk etanercept (ETN) | ETN 25 mg/wk;<br>Previous dose: 50 mg/wk for 3 mo<br>Indirectness: No direct comparison of taper to non-tapered treatment. | 25 mg/wk of etanercept per week is effective at maintaining remission.<br>Values at completion of 50 mg/wk and after 25 mg/wk<br>BASDAI: from 2.1 ± 1.0 to 2.1 ± 1.3<br>ESR (mm/h): from 8.7 ± 9.9 to 6.7 ± 5.5<br>CRP (mg/dl): from 0.2 ± 0.7 to 0.2 ± 0.2 |

## PICO 78: In adults with stable non-radiographic axial SpA on treatment with a biologic, is tapering of the biologic dose more effective than no tapering in improving outcomes?

*Guidance to voters: This is similar to PICO 65, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study. Among the studies addressing this question in AS (PICO 65), Plasencia 2015, included 9% with nr-axSpA per ASAS criteria, but results were not reported separately for this cohort.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 66: In adults with stable AS on treatment with a biologic, is discontinuation of the biologic more effective than no discontinuation in improving outcomes?

Summary: This PICO question was not directly addressed by any study. This PICO question was indirectly addressed by one RCT (Deng 2013)[82], which examined discontinuation versus the use of a DMARD as the comparator. Five observational studies also contributed indirect data that was relevant to this PICO (Brandt 2003, Baraliako 2004, Deng 2013, Breban 2002, Heldman 2011, Zhao 2017)[35,82,150-153]. An additional study included <40% AS patients (Song 2012)[154], and is reported in PICO 79, which addressed this question in nr-axSpA patients.

Overall, results from the observational studies suggest that discontinuation of TNFi results in a high rate of flares... [see table below]

Overall quality of evidence across all critical outcomes: Very low to Low

### Table 1. Observational Data Summary (all indirect evidence)

| REF ID, Author, year | Study type | Duration (wks) | Risk of Bias | Main point estimate | Indirect | Imprecision | Consistency | Quality of evidence | N | Flare/ Relapse % | Dz duration (yrs) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2571, Breban 2002[151] | Observational | 24 | serious | GAP/ASAS20 | no control | Serious (measures of dispersion missing from multiple studies | Not serious | Very low | 48 | 73 | Median 13 |
| 2532, Brandt 2003[35] | Observational | 36 | serious | BASDAI | vs. baseline; not stable pts | | | | 26 | 100 | 14.9 |
| 2386, Baraliakos 2004[150] | Observational | 48 | serious | BASDAI | vs. baseline, no control | | | | 42 | 98 | 15 |
| 1306, Deng 2013[82] | RCT | 52 | serious | BASDAI | Compared to DMARD, no continuation of TNFi | | | | 111 | 79 | 9 |
| 1533 ,Heldmann, 2011 [152] | Observational | Mean 64 | serious | BASDAI | | | | | 14 | 64 | ----- |
| 4059, Sebastian 2017[155] | Observational | 36+ | serious | BASDAI | vs. baseline, no control | | | | 54 | 74 | N/A |
| 23, Zhao 2017[153] | Observational | 52 | serious | BASDAI | vs. baseline, no control | | | | 35 | 46 | 7.7 |
| | | | | | | | | **Total/Mean** | **330 Patients** | **76.3%** | **7.7** |

## Table 2. Descriptive Summaries of Studies (all indirect evidence)

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 4059, Sebastian 2017[155] | Observational study | 9 to 40 months | 65 patients with axial SpA | Discontinuation of TNFi therapy after achieving low disease activity | Relapse: 40 patients (74% of patients with low disease activity [LDA]) had an increase of the disease activity after a mean of 14 weeks<br>LDA was regained in all patients after a mean of 7 weeks after re-starting TNFi therapy |
| 23, Zhao 2017[153] | Observational follow-up | 3 years | 35 pts with AS who achieved ASAS 20 remission with ETN | Discontinuation of etanercept following remission | Relapse: 21 of the 35 (60.0%) patients relapsed after withdrawal of etanercept<br>Median time of relapse was 15 months (IQR, range 3.7 to 26.3 months) |
| 1306, Deng 2013[82] | Randomized trial | 1 yr max; avg follow-up 5.1 ± 3.9 mo. | 111 AS patients achieving ASAS20 response after treatment with etanercept | Thalidomide (150 mg/day); sulfasalazine (1 g, 2x daily); or NSAIDs | Regardless of maintenance treatment, most patients terminating etanercept treatment experienced disease recurrence.<br>Recurrence rates:<br>NSAIDs: 33 of 37 patients (89.2%).<br>Sulfasalazine: 28 of 33 (84.8%)<br>Thalidomide: 18 of 30 (60%) |
| 1533, Heldmann 2011[152] | RCT/observational | Mean 1.3 years | 103 patients (n=14 with treatment withdrawn) | Discontinue/continue IFX | 9 of 14 patients (64.3%) who had IFX withdrawn after primary study experienced AS relapse |
| 2386, Baraliakos 2005[150] | Single-arm observational study | 1 yr F/U after discontinuation | 42 patients with AS | Discontinuation of infliximab after 3 years of treatment | Increase in BASDAI after drug discontinuation to the time or relapse was 3.6 (± 1.7).<br>Mean time between discontinuation and relapse was 17.5 weeks (±7.9 weeks, range 7 to 45) and the median time was 15 weeks.<br>By 3 weeks after the last patient reached relapse, 41 of the 42 patients had resumed treatment with IFX (the first patient relapsed at 7 weeks; the last patient more than 52 weeks).<br>41 patients who were reinfused responded well to the restart of therapy with infliximab. BASDAI improved from 6.1 ± 1.4 to 3.2 ± 2.6 by 6 weeks after and to 2.9 ± 2.1 by 12 weeks after reinfusion. |
| 2532, Brandt 2003[35] | RCT/ Observational | 24 weeks (observational phase) | 38 patients with active AS | Discontinuation of etanercept (ETN);<br>all patients removed from ETN after 12 weeks treatment with ETN | Relapse: 18 of these 24 patients (75%) experienced a relapse after cessation of ETN treatment.<br><br>Mean (SD) time to relapse was 6.2 (3.0) weeks. The remaining 6 patients (25%) relapsed later. |
| 2571, Breban 2002[151] | Observational study | 6 mo | 50 patients with active AS | Infliximab (3 infusions 5mg/kg at weeks 0, 2 and 6) | Relapse, defined as equal or greater than 50% loss of maximal GAP improvement, occurred in 73% of patients completing treatment. Median delay of 14 weeks after last infusion. |

## PICO 79: In adults with stable non-radiographic axial SpA on treatment with a biologic, is discontinuation of the biologic dose more effective than no discontinuation in improving outcomes?

*Guidance to voters: This is similar to PICO 66, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study. This PICO question was indirectly addressed by two observational studies, Song 2012[156], which included 65% nr-axSpA patients and 35% AS, as well as Haibel 2013[157], which was comprised entirely of nr-axSpA patients.

Overall quality of evidence for all critical outcomes: Low

### Table 1. Observational Data Summary (direct evidence)

| REF ID, Author, year | Study type | Duration (wks) | Risk of Bias | Main point estimate | Indirect | Imprecision | Consistency | Quality of evidence | N | Flare/ Relapse % | Dz duration (yrs) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1213, Haibel 2013[157] | Observational | 2 years | serious | ASAS40 | vs. baseline, no control | Serious (measures of dispersion not provided; small enrollments | Not serious | Very low | 24 | 79 | NR |
| 1437, Song 2012[156] | RCT/ Observational | 2 years | serious | BASDAI | vs. baseline, no control, includes AS, small numbers | | | | 17 | 76 | <5 |
| | | | | | | | | **Total/Mean** | **41 Patients** | **77.5%** | **----** |

### Table 2. Descriptive Summaries of Studies (direct evidence)

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 1213, Haibel 2013[157] | Single-arm observational study | 2 years | 46 patients with active non-radiographic SpA | Adalimumab followed by withdrawal of treatment for patients achieving ASAS40 | Disease flares: 19 of 24 patients (79%) experienced a flare after discontinuing adalimumab<br><br>Mean (SD) time until flare: 14.7 (5.5) weeks (range 3 to 27 weeks)<br><br>4 of 24 patients (17%) remained in good clinical condition (defined as continuous ASAS40 response without further treatment) during a 1-year observation period. |
| 1437, Song 2012[156] | RCT/ observational study | 2 years | 86 patients with axial SpA and symptom duration of <5 yrs | Patients initially treated with etanercept (ETA) or sulfasalazine (SSZ)<br><br>Patients reaching ASAS plus MRI remission at 48 weeks discontinued their treatments and were followed up to 2 years. | Most patients in both groups relapsed after drug discontinuation.<br>Number of patients remaining in drug-free remission during year 2 was not clearly different between the two groups: 3 out of 13 (23.1%) in the ETA group and 1 out of 4 (25%) in the SSZ group. Mean time to flare was not significantly different in the ETA group (24.4 weeks) and the SSZ group (39.6 weeks). |

## PICO 67: In adults with active AS, is a treat-to-target strategy using a target of ASDAS <1.3 (or <2.1) more effective than a symptom-prompted treatment strategy in improving outcomes?

Summary: This PICO question was not directly addressed by any studies. The literature search identified one RCT by Breban et al. that contributed indirect evidence. This study compared continuous to on-demand treatment with infliximab for patients with AS. Continuous treatment was every 6 weeks and on-demand treatment was given upon symptom recurrence. Both groups were given infusions of infliximab at weeks 4, 6, and 10. Patients in the on-demand group were also randomized to receive methotrexate (MTX) in combination with infliximab or infliximab alone. This study enrolled adults with AS and active inflammation in the 3-months prior to enrollment (BASDAI score >= 3 of 10 and a score of >=3 of 10 for axial pain). DMARDs were discontinued and dosages of NSAIDs/corticosteroids held stable for 4 weeks before enrollment. For most major outcomes, results indicated that efficacy of continuous treatment with infliximab was superior to on-demand treatment. However, strength of evidence for all outcomes was rated as 'low', primarily due to a limited data from a single, moderately-sized study (imprecision).

Though not formally reviewed as evidence in this report, we provide the citation for the 2017 guidelines for axial and peripheral spondyloarthritis by Smolen et al. These note that evidence for the benefit of treat-to-target strategy over routine care has been obtained for PsA in the TICOPA trial, but not for axial SpA. While recommending that the treat-to-target approach may be beneficial for axial SpA, they noted two clinical studies, one on going and one recently completed, that will help address this evidence gap for axial SpA (TICOPSA [NCT 03043846] and STRIKE [NCT 02897115] studies).

In addition, four observational studies have demonstrated the relationship of ASDAS to radiographic progression (using the mSASSS) in both AS and nr-axSpA (Ramiro 2014, Maas 2016, Poddubnyy 2016; Molnar 2018)[158-161].

Overall quality of evidence for all critical outcomes: Low

### Table 1: On-demand compared to continuous treatment with infliximab for adults with active AS

**Table 1: On-demand compared to continuous treatment with infliximab for adults with active AS**
**Bibliography: Breban 2008 [118]**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With continuous treatment | With On-demand, 58 wks | | Risk with continuous treatment, 58 wks | Risk difference with On-demand |
| ASAS20 response (58w) | | | | | | | | | | | |
| 247 (1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⊕⊕◯◯ LOW | 93/124 (75.0%) | 56/123 (45.5%) | **OR 0.28** (0.16 to 0.48) | 750 per 1,000 | **293 fewer per 1,000** (426 fewer to 160 fewer) |
| ASAS40 response, 58w | | | | | | | | | | | |
| 247 (1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⊕⊕◯◯ LOW | 63/124 (50.8%) | 37/123 (30.1%) | **OR 0.42** (0.25 to 0.70) | 508 per 1,000 | **206 fewer per 1,000** (303 fewer to 88 fewer) |
| Partial remission, 58w | | | | | | | | | | | |
| 247 (1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⊕⊕◯◯ LOW | 34/124 (27.4%) | 9/123 (7.3%) | **OR 0.21** (0.10 to 0.46) | 274 per 1,000 | **201 fewer per 1,000** (238 fewer to 126 fewer) |
| Assessment of pain (0-10 scale), 58 wks | | | | | | | | | | | |
| 247 (1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⊕⊕◯◯ LOW | 124 | 123 | - | - | MD **1.7 higher** (1.03 higher to 2.37 higher) |
| Change in patient global assessment (0-10 scale), 58w | | | | | | | | | | | |
| 247 (1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⊕⊕◯◯ LOW | 124 | 123 | - | - | MD **1.3 higher** (0.64 higher to 1.96 higher) |

| Table 1: On-demand compared to continuous treatment with infliximab for adults with active AS<br>Bibliography: Breban 2008 [118] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Certainty assessment | | | | | | | Summary of findings | | | | |
| BASDAI (change), 58w | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⊕⊕◯◯<br>LOW | 124 | 123 | - | - | MD **1.2 higher**<br>(0.65 higher to 1.75 higher) |
| BASFI change, 58w | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⊕⊕◯◯<br>LOW | 124 | 123 | - | - | MD **1.2 higher**<br>(0.66 higher to 1.74 higher) |
| SF-36 Physical component, 58w | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [d] | none | ⊕⊕◯◯<br>LOW | 124 | 123 | - | - | MD **0.3 lower**<br>(2.45 lower to 1.85 higher) |
| Schober test, cm, 58w | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [d] | none | ⊕⊕◯◯<br>LOW | 124 | 123 | - | - | MD **0.3 lower**<br>(0.64 lower to 0.04 higher) |
| Fingers to floor distance, cm, 58w | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⊕⊕◯◯<br>LOW | 124 | 123 | - | - | MD **3.8 higher**<br>(0.62 higher to 6.98 higher) |
| Occiput to wall distance, cm, 58w | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [c] | none | ⊕⊕◯◯<br>LOW | 124 | 123 | - | - | MD **1.4 higher**<br>(0.43 higher to 2.37 higher) |
| Chest expansion, cm, 58w | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [d] | none | ⊕⊕◯◯<br>LOW | 124 | 123 | - | - | MD **0**<br>(0.41 lower to 0.41 higher) |
| Death, 58w | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [e] | none | ⊕⊕◯◯<br>LOW | 0/124 (0.0%) | 1/123<br>(0.8%) | **OR 3.05**<br>(0.12 to 75.57) | 0 per 1,000 | **0 fewer per 1,000**<br>(0 fewer to 0 fewer) |
| Cancer | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [f] | | ⊕⊕◯◯<br>LOW | 1/124 (0.8%) | 1/123<br>(0.8%) | **OR 1.01**<br>(0.06 to 16.30) | 8 per 1,000 | **0 fewer per 1,000**<br>(8 fewer to 109 more) |
| Serious infection, 58w | | | | | | | | | | | |
| 247<br>(1 RCT) | not serious | not serious [a] | serious [b] | serious [e] | none | ⊕⊕◯◯<br>LOW | 3/124 (2.4%) | 4/123<br>(3.3%) | **OR 1.36**<br>(0.30 to 6.19) | 24 per 1,000 | **8 more per 1,000**<br>(17 fewer to 109 more) |

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

### Explanations

a. Not applicable; single study
b. Indirect comparison
c. Single study
d. Single study. 95% CI overlaps line of no difference.
e. Single study; very low rate of occurrence. 95% CI very wide and span line of no difference.
f. Single study; very low rate of occurrence. Point estimate at no difference.

## PICO 80: In adults with active non-radiographic axial SpA, is a treat-to-target strategy using a target of ASDAS <1.3 (or <2.1) more effective than a symptom-prompted treatment strategy in improving outcomes?

*Guidance to voters: This is similar to PICO 67, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 68: In adults with stable AS, is obtaining a spinal or pelvis MRI to confirm inactivity more effective than not obtaining an MRI in improving outcome?

Summary: This PICO question was not directly addressed by any study. Though a considerable literature documents correlations between MRI findings and disease progression, we found no studies that address the effects of obtaining spinal or pelvic MRI on patient outcomes. Furthermore, at least two studies based on data from RCTs suggest a poor correlation between achievement of clinical remission after treatment with TNFi and a lack of MRI evidence of inflammation (Braun 2017 and Lambert 2007)[32,162].

Though not provided as evidence in this report, the management recommendations by Mandl et al.[163] provide evidence-based guidance on the use of imaging in diagnosis and management of spondyloarthritis. Regarding monitoring of activity for axial SpA, these guidelines state, "MRI of the SI joints and/or the spine may be used to assess and monitor disease activity in axial SpA, providing additional information on top of clinical and biochemical assessments. The decision on when to repeat MRI depends on the clinical circumstances. In general, STIR sequences are sufficient to detect inflammation and the use of contrast medium is not needed." The citation for these recommendations are provided below.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 81: In adults with stable non-radiographic axial SpA, is obtaining a spinal or pelvis MRI to confirm inactivity more effective than not obtaining an MRI in improving outcomes?

*Guidance to voters: This is similar to PICO 68, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study. Observational studies (Maksymowych 2016)[58] of MRI at 0 and 12 weeks during treatment with TNFi have demonstrated that declines in formal MRI assessment scores (SPARCC scoring of SIJs) correlate moderately with various patient reported outcomes at 48 weeks based on data from an RCT. For example, Δ SPARCC SIJ demonstrate Spearman correlations of 0.58 with ASDAS, 0.42 with BASDAI, and 0.35 with BASFI. The strength of this association was roughly similar to that of change in CRP between 0 and 12 weeks.

More indirect evidence is available from an observational analysis (post-hoc analyses of an RCT), which demonstrate that nr-axSpA patients with baseline sacroiliitis on MRI of the SIJ respond to golimumab, whereas those without sacroiliitis, do not (Sieper 2016)[54]. However, these MRIs were not performed to evaluate for inactivity in stable patients. These findings were replicated in an observational study of the DESIR cohort comprised of mainly nr-axSpA, though ~30% of the study population exhibited radiographic sacroiliitis (Molto 2014)[164].

Overall quality of evidence for all critical outcomes: Very Low

## PICO 69: In adults with AS of unclear activity while on a biologic, is obtaining a spinal or pelvis MRI to assess activity more effective than not obtaining an MRI in improving outcomes?

Summary: This PICO question was not directly addressed by any study. This PICO question was addressed with indirect evidence from one prospective observational study (Carmona 2013)[165] and one observational cohort study (Maksymowych 2017)[166]. The prospective study compared diagnostic certainty and treatment recommendations before and after performing MRI of the spine and sacroiliac joints in patients with, or suspected of having, axial SpA. This study only measured changes in treatment recommendations and did not actually compare patient outcomes with and without use of MRI. Also, some patients did not meet standard criteria for diagnosis of axial SpA. Minimum inclusion criteria for MRI referral were patient back pain, some diagnostic uncertainty regarding the cause of back pain, and presence of active inflammation. The study included patients who did not meet the mNY criteria, patients with established axial SpA with ongoing back pain on uncertain cause (i.e., mechanical or inflammatory), and axial SpA patients with inadequate response to therapy. Twenty-two of 55 patients (40%) had changes in recommendations for or against use of biologic agents following MRI. No significant difference was found in the number of patients for whom treatment with biologics was recommended before and after MRI. Of patients recommended for TNFi therapy before MRI, 52% had this recommendation overturned after MRI. Conversely, 31% of patients not recommended for TNFi therapy before MRI were recommended for TNFi therapy after MRI. Serious concerns with bias, indirectness, and imprecision (from a single study with very small enrollment) all contributed to a very low overall strength of evidence rating.

One observational study (Maksymowych 2017)[166] has demonstrated SI joint ankylosis and fat metaplasia on MRI (but not inflammatory lesions) is associated with radiographic progression in the spine (mSASSS). Again, the effect of obtaining MRIs with these findings on patient-reported outcomes is not described. Furthermore, a small observational study (Rudwaleit 2007)[167] demonstrated that baseline MRI sacroiliitis is not associated with likelihood of BASDAI 50 response at 12 weeks, whereas baseline Berlin MRI spine score was higher in BASDAI 50 responders compared to non-responders (though there was substantial overlap between groups). Another observational study (Pedersen 2010)[168] identified a moderate association (Spearman of 0.42) of baseline Berlin MRI SIJ sacroiliitis and change in ASDAS after 22 weeks; a similar association was not found with baseline Berlin MRI spinal score. A small observational study failed to establish any correlations between SPARCC spine or SPARCC SIJ MRI scores and clinical disease activity measures (Lau 2017)[169].

Though not provided as evidence in this report, the management recommendations by Mandl et al.[163] provide evidence-based guidance on the use of imaging in diagnosis and management of spondyloarthritis. Regarding monitoring of activity for axial SpA, these guidelines state, "MRI of the SI joints and/or the spine may be used to assess and monitor disease activity in axial SpA, providing additional information on top of clinical and biochemical assessments. The decision on when to repeat MRI depends on the clinical circumstances. In general, STIR sequences are sufficient to detect inflammation and the use of contrast medium is not needed." The citation for these recommendations are provided below.

Overall quality of evidence for all critical outcomes: Very Low

## PICO 82: In adults with non-radiographic axial SpA of unclear activity while on a biologic, is obtaining a spinal or pelvis MRI to assess activity more effective than not obtaining an MRI in improving outcomes?

*Guidance to voters: This is similar to PICO 69, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study. Very indirect evidence related to this issue is available from two observational studies. One cross-sectional study (from baseline RCT data) demonstrated the presence of erosions on MRI in 11% of patients with normal/inconclusive pelvic films and no osteitis on pelvis MRI (Maksymowich 2017)[170]. This same RCT produced longitudinal data demonstrating a weak correlation between the presence of baseline erosions and backfill on MRI with change in BASDAI and ASDAS-CRP at 12 weeks (Maksymowych 2018)[171]. Observational data from the placebo arm of a TNFi RCT (Baraliakos 2017)[172] revealed that new MRI changes can appear within 12 weeks: among the 29 patients who had a normal MRI result for both the SIJs and the spine at baseline but who were judged to have active disease, 9 (31.0%) had a positive MRI result in either the SIJs or spine at week 12. Among 54 patients who had a normal MRI result for the SIJs at baseline, 5 (9.3%) had a positive MRI result for the SIJs at week 12, whereas, among 43 patients who had a normal MRI result for the spine at baseline, 11 (25.6%) developed a positive MRI result for the spine at week 12.

Overall quality of evidence for all critical outcomes: Very Low

### Table 1. Observational Data (indirect evidence)

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 110, Baraliakos 2017[172] | Post-hoc analysis of RCT data (ABILITY-1 study) | 12 wk | 94 patients with nr-axSpA who received placebo | MRI of SI joint and spine<br><br>Only data from placebo-treated patients in ABILITY-1 were analyzed<br><br>Indirectness: not a direct comparison between use of MRI and no MRI; no health outcomes data | Patients with normal MRI of the SI joint and spine at baseline (n=29): n=9 (31.0%) had a positive MRI result in either the SIJ or spine at week 12<br><br>Patients with normal MRI of the SI joint at baseline (n=54): n=5 (9.3%) had a positive MRI result for the SIJs at week 12<br><br>Patients with normal MRI of the spine at baseline (n=43): n=11 (25.6%) developed positive MRI for the spine at week 12. |
| 70, Maksymowych 2017[170] | Post-hoc analysis of RCT data (EMBARK study) | 104 wk | 185 patients with active nr-axSpA and inadequate response to 2 or more NSAIDs<br><br>(n=183 with SI joint and bone marrow edema [BME] results) | T1 weighted spin echo (WSE) MRI<br><br>Original RCT investigated efficacy of etanercept<br><br>Indirectness: not a direct comparison between use of MRI and no MRI; no health outcomes data | MRI structural lesions in patients with vs. without SIJ/BME:<br>erosions: 45.3% vs 10.9%; p<0.001<br>backfill: 20.3% vs 0%; p<0.001<br>fat metaplasia: 10.9% vs 1.8%; p=0.04<br>ankylosis: 2.3% vs 1.8%; p=ns<br><br>SIJ structural lesions (esp. erosions) may be present on MRI when radiographs are normal or inconclusive, even in patients negative for MRI SIJ inflammation. |

## PICO 70: In adults with active or stable AS on any treatment, is obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) more effective than not obtaining scheduled radiographs in improving outcomes?

Summary: This PICO question was not directly addressed with any study. Six studies (seven publications) provided indirect evidence for this PICO question, clarifying that progression can be documented in a 2 year interval; 5 studies show that 20 to 48 percent of AS patients demonstrate progression of an ≥2 mSASSS over 2 years. From among these, an observational study (Poddubnyy 2016)[173] followed 60 AS patients with mSASSS performed biennially. After the initial improvement, BASFI and BASMI remained remarkably stable at low levels over up to 10 years despite radiographic spinal progression.

Data for SIJ radiographic progression is presented for comparison: a very brief report (Sepriano 2016)[174] from the ASAS cohort compared the percentage meeting mNY Criteria (based on SI joint films) at baseline and then after a mean of 4.4 years, finding that a net of 5% had progressed (of those initially classified as meeting mNY Criteria, 58% no longer met criteria based on a read of the second set of films). A similar study by (Poddubnyy 2011)[175] identified a progression rate from non-radiographic axial spondyloarthritis to AS of 11.6% over 2 years.

Though not formally reviewed as evidence in this report, we provide a citation for the 2017 guideline recommendations for axial and peripheral spondyloarthritis by Smolen et al. These guidelines note that imaging results, including those from conventional radiography, MRI and sonography, may be considered in clinical management. They state, "While imaging is not recommended as a target, it may assist where there is doubt if a target has been reached (i.e., if the target was not reached because of inflammation or other reasons)."

Overall quality of evidence for all critical outcomes: Very Low

### Table 1. Summary of mSASSS Progression

| Ref ID, Author, year | Duration | Population Description | Rate mSASSS units/yr | % progression ≥2 mSASSS over 2 yrs | % progression ≥5 mSASSS over 2 yrs |
|---|---|---|---|---|---|
| **14, Park 2017[176]** | 2 yr | N=31 patients; 20 male patients with AS; 11 gender, age-matched controls | 1.25 (median) | 35 | ------- |
| **265, Maas 2016[177]** | 4, 6, 8, 10 yr F/U | N=210 AS pts with active disease who started TNFi treatment; largest numbers reported at 4 yr F/U (results in this table reflect this timepoint) | 0.88 | 25 | ------- |
| **220, Podubbnyy 2016[173]** | 10 yr | N=60 patients; from 2 long-term open-label TNFi extensions of clinical trials | 0.6 | ------- | ------- |
| **4000, Ramiro 2013[178]** | 12 yr (every 2 yrs) | N=186 patients with AS (n=68 completers of 12 yrs); 95% of patients were treated with NSAIDs and 22% to TNFi (only 5% exposed to TNFi before year 8). | 0.98 | 48 (1st 2 yr F/U) 29 (all 2 yr F/U) | 25 (1st 2 yr F/U) |
| **4216 Podubbnyy 2012[179]** | 2 yrs | N=210 patients with axial SpA (GESPIC Cohort) | 0.95 | 20 | ------- |

### Table 2. Additional Observational Data

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| 3247 Sepriano 2016[174] | Observational | Mean 4.4 yrs | 357 pts with chronic back pain or undiagnosed peripheral symptoms | Pelvic radiographs | 62 of 357 (17.4%) satisfied criterial for r-axialSpA at baseline vs. 80 of 357 (22.4%) at follow-up.<br><br>36/62 (58.1%) considered mNY-positive at baseline were mNY-negative at follow-up |
| 4217, Poddubnyy 2011[175] | Observational | 2 yrs | N=210 patients with axial SpA | Radiographs of SI joints | 115 patients (54.8%) met modified NY criteria for AS in opinion of both readers at baseline; 95 patients (45.2%) were classified non-radiographic.<br>Rate of progression from non-radiographic axial spondyloarthritis to AS was 11.6% over 2 years. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Mean rate of progression of radiographic sacroiliitis at 2 years was low: 0.07 (95% CI −0.05 to 0.19) and 0.09 (95% CI −0.03 to 0.21) grades for the left and right SI joints, respectively |

## PICO 83: In adults with active or stable non-radiographic axial SpA on any treatment, is obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) more effective than not obtaining scheduled radiographs in improving outcome?

*Guidance to voters: This is similar to PICO 70, which posed the same question in AS.*

Summary: This PICO question was not directly addressed by any study. Indirect evidence is available from 5 observational studies (six publications).

Two reports based on the GESPIC observational cohort (Poddubnyy 2012 and Poddubnyy 2011)[175,179] reported definite radiographic progression (≥2 mSASSS unit increase) in 7.4% of nr-axSpA patients over the initial 2 years of follow-up.

To contrast, data are reported regarding the progression from nr-axSpA to AS (mNY criteria) at the SIJ for 5 studies. Roughly 2 to 8% progressed per year and 20-30% over 10 years.

As is the case with PICO 70 above, we provide a citation for the 2017 guideline recommendations for axial and peripheral spondyloarthritis by Smolen et al.

Overall quality of evidence for all critical outcomes: Very Low

### Table 1. Observational Data Summary (indirect evidence)

| Ref ID, Author, year | Study type | Duration | Population Description | Treatment given to relevant population | Results |
|---|---|---|---|---|---|
| **Spinal radiographs** | | | | | |
| 4216, Poddubnyy 2012[179] | Observational | 2 yr | 210 patients with axial SpA<br>(n=95 with nr-axSpA; n=115 with AS)<br>*Note: Same cohort as ref 4217 below | Spinal radiographs scored by 2 blinded readers<br>Indirectness: no direct comparison (radiographs vs. no radiographs); pelvic radiographs, not spinal; only 45% nr-axSpA | Radiographic progression (2 yrs): 7.4% (95% CI 3.6 to 14.4%) of patients with nr-axial SpA (vs. 20% of patients with AS; 14.3% over all patients)<br>Mean mSASSS: increased significantly for nr-axSpA patients, from 2.30 ± 4.24 at baseline to 2.76 ± 5.26 after 2 years (p=0.01); difference = 0.46 ± 1.63 units (Spinal radiographic progression defined as worsening of mean mSASSS by >2 units.) |
| **Pelvic Radiographs** | | | | | |
| 3184, Christiansen 2017[180] | Observational | 2 yr | 104 consecutive patients with suspected axial SpA<br><br>(78% met ASAS criteria) | Pelvic radiographs by 7 blinded readers (2 musculo-skeletal radiologists, 5 rheumatologists)<br>Indirectness: no direct comparison (radiographs vs. no radiographs); pelvic radiographs, not spinal; not all Ps with axial SpA | Over all 7 readers, a mean of 15.7% patients met the modified NY criteria (mNY), and 8.1% showed mNY grades 3 or 4 |
| 402, Dougados 2016[181] | Observational | 2 yr | 449 patients with axial SpA (n=326, 73%, with nr-axial SpA | Pelvic radiographs by 2 readers blinded to patient information<br>Indirectness: no direct comparison (radiographs vs. no radiographs); pelvic radiographs, not spinal; not all Ps with axial SpA | Mean change SI joint score (range 0–8): 0.1 ± 0.8 (p < 0.001)<br>Switch from nonradiographic to radiographic axial SpA: 4.9% (16 of 326) |
| 487, Wang 2016[182] | Cohort study | 10.6 ± 5.6 years | 83 patients with new-onset nr-axSpA | Pelvic radiographs<br><br>Indirectness: two arms (imaging vs. clinical) assigned according to how | Progression to AS: significantly more frequent in the imaging arm (28% vs. 17% for clinical arm)<br>Median time to progression to AS: 4.8 years for imaging arm vs. 6.8 years for clinical arm (hazard ratio of 3.50 (95% CI 1.15 to 10.60; p=0.02). |

| | | | | | |
|---|---|---|---|---|---|
| | | | | diagnosed, not randomly assigned; pelvic, not spinal, radiographs | |
| 4217, Poddubnyy 2011[175] | Observational | 2 yr | 210 patients with axial SpA;<br>n=95 (45.2%) nr-axSpA | Radiographs of SI joints<br>Indirectness: no direct comparison (radiographs vs. no radiographs); pelvic radiographs, not spinal; only 45% nr-axSpA | 10.5% of patients with nr-axSpA compared to 4.4% with AS showed an estimated 'true' progression by at least one grade according to both readers<br>Rate of progression from non-radiographic axial spondyloarthritis to AS: 11.6% over 2 years |
| 4215, Sampaio-Barros 2010[183] | Prospect observational | 2 to 10 yrs | 111 patients with uSpA | Pelvic + calcaneal radiographs<br>Indirectness: no direct comparison (radiographs vs. no radiographs); radiographs were not spinal | Disease progression: 27 pts (24.3%) progressed to AS; 3 (2.7%) to psoriatic arthritis; 25 pts (22.5%) went into remission |

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