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The Effect of Therapy on Radiographic Progression in Axial Spondyloarthritis: A Systematic Review and Meta-Analysis

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Abstract

Objectives: To investigate effect of therapies on radiographic progression in axial spondyloarthritis (axSpA).

Methods: Comprehensive database search for studies assessing radiographic progression in axSpA (particular treatment vs. no treatment of interest) was performed. Study-specific standardized mean differences were estimated and combined using random-effects model.

Results: Twenty four studies were included; 18 with tumor necrosis factor inhibitors (TNFi), 8 with non-steroidal anti-inflammatory drugs (NSAIDs), and 1 with secukinumab. Spinal radiographic progression was not significantly different among TNFi-treated vs. biologic naïve populations at 2 years (mSASSS difference= −0.73, 95% CI −1.52 to 0.12, I^2=28%) and at ≥4 years (mSASSS difference= −2.03, 95% CI −4.63 to 0.72, I^2=63%). Sensitivity analysis restricted to studies with low risk of bias showed a significant difference at ≥4 years (mSASSS difference= −2.17, 95% CI −4.19 to −0.15). No significant difference was observed between NSAIDs vs. control (mSASSS difference= −0.30, 95% CI =−2.62 to 1.31, I^2=71%), or secukinumab vs. biologic naïve (mSASSS difference= −0.34, 95% CI −0.85 to 0.17). There were not enough studies on nr-axSpA or SIJ progression for analysis.

Conclusions: Although no significant protective effect of TNFi treatment on spinal radiographic progression of AS at 2 and ≥4 years was seen, analysis restricted to studies with low risk of bias

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showed a protective effect at ≥4 years. Therefore, long-term TNFi exposure might have radiographic progression benefit. No difference was seen with NSAIDs or secukinumab at 2 years. Future studies should explore effect of biologics on radiographic progression in early axSpA and nr-axSpA, and with long-term exposure.

Keywords

spondyloarthritis; ankylosing spondylitis; radiographic progression; TNF inhibitor; NSAIDs

INTRODUCTION

Treatment goals for axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA), are control of spinal and peripheral symptoms as well as prevention of radiographic damage [1]. Radiographic progression takes place in 20–45% of AS patients after 2 years and progression is expected to continue in successive years, leading to complete fusion of spine ("bamboo spine") in up to 40% of patients with AS [2,3]. Rate of progression is slower in nr-axSpA, about 7% at 2 years [3].

Conventional radiography is the gold standard for assessment of radiographic progression [4], although magnetic resonance imaging can detect active inflammation before changes due to chronic damage appear on radiograph [5]. Assessment of SpondyloArthritis international Society(ASAS) and Outcome Measures in Rheumatology (OMERACT) Working Groups recommend use of modified Stoke AS Spine Score (mSASSS) for quantitative assessment of axial damage [6,7]. mSASSS ranges from 0 to 72, signifying structural changes on lateral radiographs of cervical and lumbar spine [8]. It that has the highest reliability and greatest validation compared to Bath AS Radiology Index (BASRI) and sacroiliac joint (SIJ) scores [6,7,9]. The minimum interval for significant radiographic change is 2 years [10,11], and a change of 2 mSASSS units in 2 years or 1 new syndesmophyte formation in 2 years is considered as radiographic progression [2,12].

Although radiographic progression is an important predictor of poor functional outcomes in axSpA [13,14], treatment is largely symptomatic at present. If any therapy is shown to slow the natural progression of disease, it might support introducing them early with treat-to-target strategy, similar to rheumatoid arthritis (RA). The current guidelines recommend against this due to lack of evidence [1].

Considering the clinical implications of radiographic progression and conflicting study results, we aimed to perform a systematic review and meta-analysis on the effect of different therapies on radiographic progression in axSpA.

METHODS

Search strategy and study selection

A comprehensive search of several databases from inception to January 15, 2019 was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane un Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. ACR and EULAR

abstracts indexed in MEDLINE were included as well. Search strategy was designed and conducted by a medical reference librarian with input from the principal investigator (Supplementary File 1).

We included all original reports fulfilling the following criteria:

1. Adults (≥18 years) with axSpA, including AS and nr-axSpA.
2. Participants were assessed for radiographic progression of axial disease (outcome) using a quantitative scoring method (mean mSASSS score, number of syndesmophytes, SIJ score, or any other scoring method).
3. Radiographic scores were reported with respect to a particular therapy and compared to placebo or a group without the therapy of interest.
4. Duration of follow-up at least 1 year.

While cohort and case-control studies were included; cross-sectional studies, case series, case reports, and non-human studies were excluded. The effect of combination therapy was beyond the scope of this study.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews [15] was followed (Figure 1). Two authors (PK and AD) screened abstracts for eligibility, retrieved full-texts and excluded irrelevant articles. The inter-rater agreement was very good (kappa statistic- 0.91, 95% CI- 0.81 to 0.99). Disagreements were resolved by discussion about eligibility. Bibliographies belonging to included studies, reviews, and relevant articles were screened for additional studies. No language restrictions were made. Language translation was done by translators proficient both in the particular language and in English (AD and EM).

Data extraction/handling methods

Relevant data were extracted by PK, and checked by RS. Data from available full texts were considered in preference to conference abstracts, unless the abstracts contained updated results. Where a matched data analysis was provided (for example, in studies with historical comparison group), this was extracted with preference to data on all participants. Data on radiographic progression were collected at 2 and ≥4 years of follow up. Authors were contacted for additional data where necessary.

Outcomes

The main outcome was difference in mSASSS in AS between groups at 2 years and ≥4 years. Other radiographic scores such as: mSASSS in nr-axSpA, change in number of syndesmophytes, BASRI-spine, CT score of the facet joints and SIJ radiographic progression in AS and/or nr-axSpA were secondary outcomes. We did not pool mSASSS with SIJ or other scores in our analysis as pooling different scoring systems has not been validated. For example, the SIJ score is semi-quantitative with relatively poor correlation with functional status [16] and inter-reader reliability [17].

The effect size measured as the standard mean difference (SMD) of the change in radiographic score from baseline between treatment and control group was used.

SMD was estimated as:

SMD= (Radiographic score $_{T,\ baseline}$ − Radiographic score $_{T,\ follow\text{-}up}$) − (Radiographic score $_{C,\ baseline}$ − Radiographic score $_{C,\ follow\text{-}up}$) divided by SD $_{Pooled}$

Where SD $_{Pooled}$ is the pooled SD of the radiographic change in treatment (T) and control groups (C) at baseline and follow-up.

Statistical analysis

All outcome comparisons and treatment effects were calculated using RevMan version 5.3. Binary measures were converted to SMD (SE) [18]. Study specific SMDs were estimated and combined using the random-effects model as described by DerSimonian and Laird[19]. Rescaling to original units (eg. mSASSS and number of syndesmophytes) was done by multiplying SMD by SD to allow better clinical interpretation. The SD was taken from the average of the pooled SD of change in radiographic scores (of the treatment and control group) from several trials reporting the original scale [20].

Radiographic outcomes in AS and nr-axSpA were reported separately and not pooled. To maintain independence, only 2 of 4 studies with the Outcome Assessment in Ankylosing Spondylitis (OASIS) cohort as control (with the largest number of patients) were included in 2 separate forest plots (one study each for 2 years [21] and >4 years [22]). Sensitivity analysis was carried out with other studies [23,24], one at a time. Similarly, 2 studies from the Prospective Study Of AS (PSOAS) cohort were included only in separate analyses [25,26]. Data from Gensler et al. [26] was used in preference to an older publication from PSOAS cohort (mSASSS was defined as mSASSS of ≥1 unit/year, and variable follow-up periods of 1.5 to 9 years) [27]. Sample mean and SD were calculated from sample size, median, range and/or interquartile range [28].

Assessment of risk of bias, certainty in the evidence and heterogeneity

Studies were independently evaluated by PK and RS for risk of bias [29]. New-Castle Ottawa scale [30] was used for cohort studies, and Revised Cochrane risk-of-bias tool (RoB 2.0) was used for randomized trials [31] (Supplementary File 2). The certainty in the evidence was evaluated using the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) methodology [32]. Publication bias was assessed visually using funnel plots (Supplementary File 3). Between-study heterogeneity was assessed using I^2 statistics (i.e., I^2 < 30% - low heterogeneity, 30 to 60%- moderate, and >60% - high) [33].

RESULTS

Characteristics of the included studies

Out of 524 studies screened, 24 studies (23 English, 1 Russian language) fulfilled our inclusion criteria: 18 studies related to TNFi (N= 4,874), 8 to NSAIDs (N= 2,321), and 1 to

secukinumab (N=237). Among these, 3 studies contained data for both NSAIDs and TNFi [25,26,34]. Included studies were mostly cohort studies and open label extensions of randomized controlled trials (RCTs). Three of the TNFi studies were excluded from the meta-analysis (details provided above in the statistical analysis section). One RCT for TNFi [35], and 2 RCTs for NSAIDs [36,37] were noted (Table 1). Most studies were judged to have low risk of bias, except 2 observational studies [38,39] and 2 RCTs [36,37] (Supplementary File 2). One study on NSAIDs [40] was excluded as no quantitative data was available and phenylbutazone (no longer approved for human use in US) was studied.

Among TNFi studies, there were 17 studies in AS and 1 study in nr-axSpA [41]. Six studies used a historical cohort as a comparator, not on TNFi (OASIS, 4 studies [20,31–33]; the German Spondyloarthritis Inception cohort (GESPIC), 1 study [42]; Herne cohort, 1 study [43]). Two studies used contemporary cohorts, not on TNFi as comparators [41,44]. The control group was on continuous NSAIDs [38], NSAIDs [44], or standard of care with no TNFi. The only RCT for TNFi used placebo as control until 24 weeks, after which they crossed over to receive golimumab 50 mg (same as the intervention arm) through 100 weeks [35]. The type of TNFi used was variable: 3 studies used infliximab [22,24,42], 2 studies etanercept [23,41], 1 study adalimumab [21], 1 study golimumab [35], 2 studies used etanercept, infliximab and adalimumab [45,46], and type of TNFi was not specified in remainder of the 7 studies. Only one of the studies compared 2 doses of TNFi (golimumab), and none of the other studies compared TNFi dose response in relation to radiographic progression [35]. Maximum duration of follow-up was 2 years in 7 studies [20,32–34,38–40], ≥ 4 years in 9 studies [22,28,31,35–37,42–44], and one study had a median follow-up of 3 years (>2 years to >10 years) [25]. The mean duration of disease was >5 years in most studies, except in 3 of the included studies [41,44,47]. Baseline mSASSS varied between studies and also within study groups, ranging from 4 to 18.87 (median= 13.20) in the TNFi group and 3.70 to 19 (median=14.20) in the control group.

Among 8 NSAID studies, there were 6 studies with only AS patients, 1 study with early axSpA [39], and 1 study with both AS and nr-axSpA [49]. Six studies reported mSASSS [26,34,36,37,39,49], 1 study BASRI spine [50], and 1 study BASRI-SIJ [25]. The maximum duration of follow-up was 2 years in 5 studies and >2 years in 3 of the studies [25,34,50]. Baseline mSASSS ranged from 6.60 to 14.20 (median= 7.90) in the NSAID group, and 5.70 to 14.20 (median=11.65) in the control group in AS patients. In one of the studies reporting nr-axSpA, the mean mSASSS was 1.60 (SD=4) compared to 2.60 (SD=4.80) [49].

The only included study (abstract) with secukinumab was a retrospective analysis of an RCT, comparing 2 year data to the historical biologic-naïve Effects of NSAIDs on Radiographic Damage in Ankylosing Spondylitis (ENRADAS) cohort [51]. mSASSS was comparable between the 2 groups: 9.55 (SD=14.14) in the secukinumab group and 9.95 (SD=13.76) in the control group. The full manuscript was published beyond the inclusion period for our review, and data from the abstract were verified with the final published version (June 2019) [52]. The original trial and 4 year data were not included in our study because while two different doses of secukinumab were compared, the study did not have a NSAID or placebo arm [53,54].

Radiographic outcomes- TNFi

In assessment of spinal radiographic progression with TNFi in AS patients, most studies reported mSASSS (15 studies) whereas one study reported a CT score of facet joints [47] (Table 2). No studies on spinal radiographic progression with TNFi in nr-axSpA were found. Five studies also measured change in number of syndesmophytes [34,38,43,45,46]. Spinal radiographic progression was not significantly different among the TNFi-treated vs. the biologic-naïve populations at 2 years (mSASSS difference= −0.73, 95% CI −1.52 to 0.12, I^2=28%) and at ≥4 years (mSASSS difference= −2.03, 95% CI −4.63 to 0.72, I^2=63%). (Figure 2A & B). However, sensitivity analysis restricted to six studies with low risk of bias (excluding one study[38]) showed a significant difference at ≥4 years (mSASSS difference= −2.17, 95% CI −4.19 to −0.15, I^2=49%) (Figure 2C). Certainty in this following the GRADE approach was low (supplemental file 2).

Conversion to mSASSS was done by multiplying the SMD by the average pooled SD (6.06 at 2 years [21,26,35,42,45,46], and 14.47 at 4 years [22,26,35,38,43,48]) as explained in the methods section. Only one of the studies reported change in CT score of facet joints, which was not significantly different between TNFi and biologic-naïve groups (CT score difference= −0.16, 95% CI −27.91 to 27.59) [47]. The largest study with OASIS as the control group [21] was included in primary analysis (one each in 2 years and ≥4 years follow-up). Sensitivity analyses performed with other studies that used OASIS as control, one at a time, did not show any difference. Subgroup analyses performed to assess heterogeneity did not reveal significant differences between historical and contemporary control groups (p=0.54). Similarly, there was no difference in the number of syndesmophytes between the TNFi and biologic-naïve groups at 2 years (SMD= −0.04, 95% CI −0.51 to 0.43; change in no. of syndesmophytes= −0.05, 95% CI −0.59 to 0.49, I^2=69%) or 8 years of follow-up (SMD= 0.34, 95% CI −0.86 to 1.55; change in number of syndesmophytes= 0.78, 95% CI −3.01 to 4.57, I^2=83%). Average pooled SD (1.15 at 2 years [45,46] and 2.29 at 8 years [38,43]) from studies reporting a change in the number of syndesmophytes was used for the conversion [46].

Only 2 studies [25,41] reported radiographic changes at the SIJ. Minhas et al. reported OR= 0.06 (95% CI= 0.004 to 0.99) for BASRI- SIJ (radiographic change in SI joint) in the PSOAS cohort for the TNFi vs. biologic-naïve groups [25]. Dougados et al. reported change in total SIJ score of −0.22 (95% CI −0.38 to −0.06, p=0.008) in TNFi vs. biologic-naïve groups in nr-axSpA [41]. Pooled estimates were not calculated for the 2 studies as the study populations were different (AS vs. nr-axSpA) (Figure 3B).

Radiographic outcomes- NSAIDs

Among 6 studies reporting mSASSS with NSAIDs in AS at 2 years, no significant difference was observed between NSAIDs vs. control group (SMD= −0.08, 95% CI −0.32 to 0.16, mSASSS difference= −0.30, 95% CI =−2.62 to 1.31, I^2=71%)[26,34,36,37,49] (Figure 4). Average pooled SD (8.18) was used for the conversion [26,36,37]. Dosing strategies for NSAIDs in both treatment and control arms were different- comparisons were made between continuous vs. on-demand [36,37], NSAID index >50 vs. <50 [49] and NSAID vs. no NSAID [26,34]. Subgroup analysis (continuous vs on-demand NSAIDs use, NSAID index-

high vs low, and NSAIDs vs no NSAIDs) of these showed no difference (p=0.79). There was one study which compared BASRI-spine for NSAID vs. control, which showed no difference as well (BASRI-spine difference= 0.020, 95% CI= −0.44 to 0.48) [50]. One study reported a subgroup of patients with nr-axSpA, in whom no difference in mSASSS was observed (mSASSS difference= 0.13, 95% CI=−0.39 to 0.65) [49]. Sensitivity analysis after removing an observational study judged to have high risk of bias [39] did not change the results.

Two studies [25,39] with NSAIDs reported changes in SIJ based on BASRI-SIJ, where no difference in SIJ radiographic progression was seen in the two groups (SMD=−0.18, 95% CI −0.65 to 0.29, SIJ score difference= −0.40, 95% CI −1.44 to 0.64, I^2=0%). Pooled SD (2.21) was used for the conversion [39].

Radiographic outcomes- secukinumab

The only included study with secukinumab, did not show a significant difference in radiographic progression over 2 years (mean mSASSS difference= −0.34, 95% CI −0.85 to 0.17) [51].

DISCUSSION

This systematic review and meta-analysis showed that TNFi may slow radiographic progression at the spine in AS at ≥4 years (when only studies judged to have low risk of bias were included) but not at 2 years. Recent studies have suggested that progression might be less beyond 2 years [55]; and a non-linear, continued benefit beyond 4 years has been observed with TNFi [26,56]. These studies adjust for important confounders (eg. smoking status, NSAID use, baseline mSASSS and disease/symptom duration), which might account for the difference in results. Our study showed a larger difference in mSASSS between TNFi and biologic-naïve group at ≥4 years, suggesting continued benefit with long-term use of TNFi. The difference in radiographic progression at SIJ in AS and nr-axSpA was not significant in each of the 2 included studies (Figure 3). The semi-quantitative nature of the SIJ score with inter-reader variability, make the study of radiographic progression at SIJ challenging.

In contrast, NSAIDs did not show any significant inhibition of radiographic progression in AS at the spine at 2 years or SIJ at >2 years. A clinically significant effect at long term follow up is possible and will require long-term studies. Furthermore, differential effects of NSAIDs have been noted, and are believed to be related to the degree of Cox-2 selectivity. Wanders et al. showed that AS patients on continuous celecoxib have lower radiographic progression in comparison to on-demand treatment over 2 years, although the cumulative dose between the groups was not much different [37]. Also the study was not blinded, and may have resulted in differential use of co-interventions such as exercise, smoking cessation, etc. In a post-hoc analysis of this trial, those with elevated acute phase reactants seemed to have the greatest benefit with continuous celecoxib compared to on-demand NSAIDs [57]. It is postulated that elevated prostaglandin E2 leads to increased osteoblastic activity, and hence inhibition of prostaglandin (especially prostaglandin E2) synthesis by Cox-2 inhibitors might inhibit new bone formation [58,59]. However, a subsequent non-blinded

RCT (ENRADAS trial) that used diclofenac, failed to confirm these findings [36]. It is unclear whether the differential effect on bone formation with selective Cox-2 inhibitors used in Wanders et al. as opposed to the non-selective NSAIDs used in ENRADAS trial led to the difference in results. At present, there is insufficient evidence to confirm the effect of NSAIDs (selective or non-selective) on radiographic progression alone or in combination with TNFi. Long-term risk of different NSAIDs in this population should be studied further in terms of cardiovascular and gastrointestinal safety to justify the risk-benefit profile.

The only study with secukinumab did not show a significant difference in radiographic progression at 2 years [51]. More studies are required to better understand the long-term effects and effects in early disease. Phase III data from secukinumab showed no increase in spinal radiographic damage in 80% of AS patients at 2 and 4 years [53,54], but these data need to be interpreted with caution in the absence of a control group.

A paucity of data on the effect of treatment on radiographic progression in nr-axSpA was noted. A subgroup of nr-axSpA from the GESPIC cohort showed no difference in mSASSS progression between high and low NSAID use at 2 years [49]. Only one study exploring the effects of TNFi on SIJ progression from the EMBARK trial was included in our study, which did not show any significant difference [41]. Study by Almirall et al. and the RAPID-axSpA study were not included in our study as all patients in these studies were treated with TNFi with no comparator arm [55,60]. These studies showed no radiographic progression at the spine/SIJ at 2 years and SIJ at 4 years, respectively. However, the data are difficult to interpret in the absence of a controlled comparison. No data on secukinumab or biologics with other modes of action was found.

Although our study showed a significant effect of TNFi on long-term radiographic progression (in sensitivity analysis), none of the included studies provide prospective, long-term controlled comparison. Most included studies were judged to have a low risk of bias; however predominance of observational and open-label extensions of RCTs limits overall level of evidence. Most analyses in our study showed low to moderate heterogeneity and a few (on NSAIDs) showed high heterogeneity. There were methodological differences in between the studies and various subgroup and sensitivity analyses, e.g., historical vs. contemporary controls, and dosing of NSAIDs were done. These explain some heterogeneity in the data, but not all.

Answering the question of radiographic progression will require a concerted effort. Long term, controlled trials of axSpA therapies are costly, therefore alternative strategies will be necessary to learn which therapies are best in preventing radiographic progression. Well-designed RCTs with head-to-head comparisons will be required to establish the comparative efficacy of biologic therapies, either alone or in combination with NSAIDs, in slowing radiographic progression. A head-to-head study of secukinumab with TNFi is planned [61], which will hopefully give us more information regarding their comparative efficacy. There is an ongoing RCT comparing radiographic progression at 2 years between treatment with TNFi alone and the combination of TNFi and NSAIDs, following promising data on the combination approach from observational studies [26]. There is also increasing evidence to suggest that TNFi in early AS (<10 years) is associated with a higher benefit. Observational

studies by Haroon et al. [27] and Park et al. [44] both suggested the importance of early initiation of TNFi therapy on radiographic progression. Data from observational studies will be limited as the expense of serial imaging tests; and using observational data to assess radiographic progression will likely require funding specifically to obtain serial imaging at standardized intervals among patients who are treated with TNFi or IL-17 inhibitors alone or in combination with NSAIDs. Secondly, risk stratification to identify those at high risk of progression is important given that not all patients progress. Risk factors for radiographic progression of axSpA noted in multiple studies are male sex, HLA-B27 positivity, baseline radiographic changes, long disease/symptom duration, high C-reactive protein, high disease activity, smoking status, [62] and more recently alcohol has been implicated [63]. Close monitoring and early therapy with a treat-to-target strategy might have a greater impact on slowing structural damage in this high risk group. Lastly, we need more sensitive and reliable measures to document radiographic progression. While most studies used mSASSS, the most validated measure for radiographic progression in AS, it is based on plain radiographs with limited sensitivity to change. mSASSS doesn't include assessment of changes at thoracic spine or posterior elements (facet joints), and cannot assess early damage [64,65]. Inter-reader reliability for mSASSS change is also of concern, with most studies showing poor to moderate reliability [21,24,52]. While plain radiography is cheap, fast, and has years of experience with reading; it might not be the best measure for assessment due to the slow nature of radiographic progression in AS. Newer measures, such as those based on quantitative low-dose computed tomography (ld-CT) scan may provide higher sensitivity in detecting small changes in syndesmophyte size/volume [66,67]. Ld-CT has also been shown to have good correlation with various measures of patient function such as Schober test and lateral thoracolumbar flexion [68]. Comparison of x-ray measurement (mSASSS) with these newer modalities will guide whether CT is an acceptable outcome for measure in clinical trials.

CONCLUSION

Although no significant protective effect of TNFi treatment on radiographic progression of AS at the spine at 2 years and 4 years was found in our study, analysis restricted to studies with low risk of bias showed a protective effect at ≥4 years. Therefore, long-term TNFi exposure might have radiographic progression benefit. No difference was seen with NSAIDs or secukinumab (only 1 study) at 2 years but long-term data were not available. Further studies should explore the effect of NSAIDs and biologics alone and in combination in patients with early axSpA; their use in the group with high risk of progression should be evaluated with a follow up >4 years to see if effects are more pronounced over time. Newer measures with higher sensitivity to detect structural changes, such as those based on quantitative low-dose CT should be compared to mSASSS for use in clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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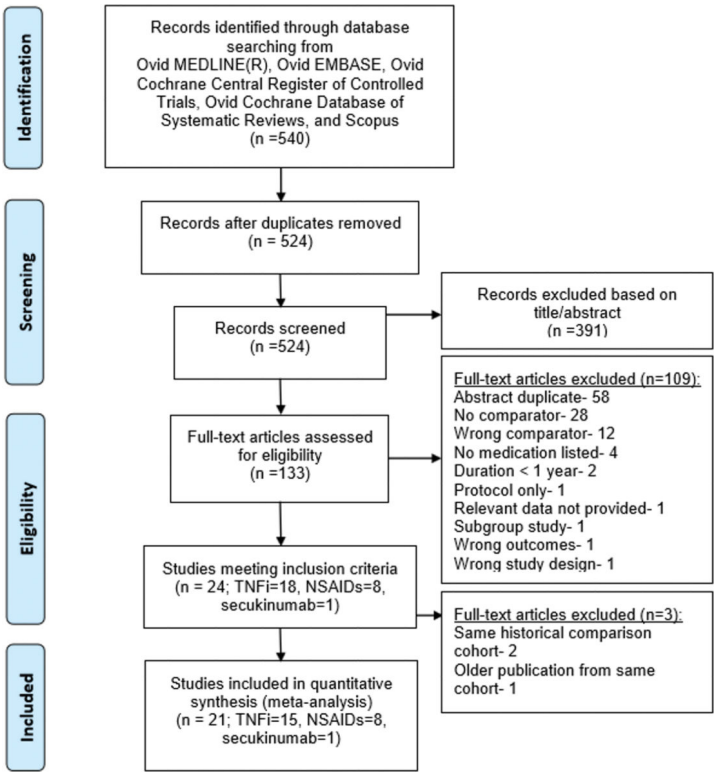

Figure 1.
Flow chart describing systematic search and study selection process

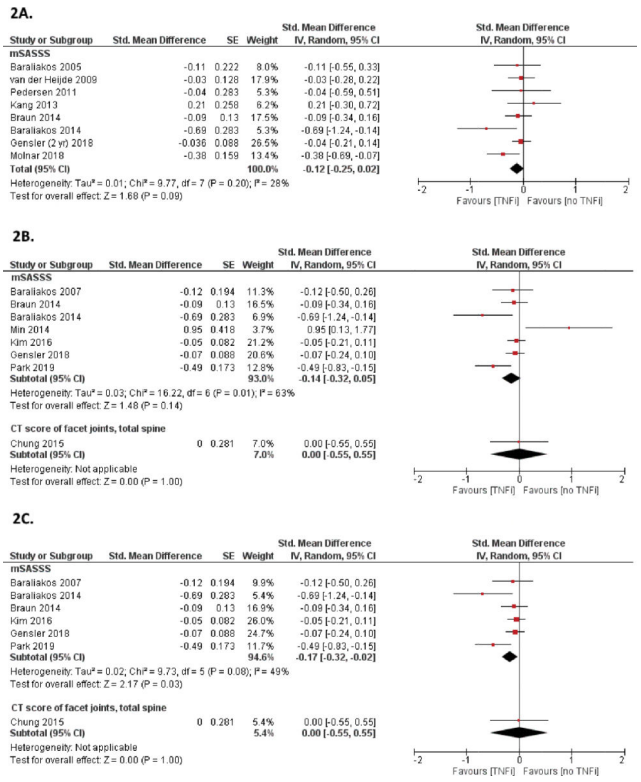

Figure 2.

Forest plot of radiographic progression in patients on tumor necrosis factor inhibitor alpha (TNFi) A) radiographic progression at the spine in AS- 2 years, B) radiographic progression at the spine in AS- ≥ 4 years, C) sensitivity analysis with low risk of bias studies for radiographic progression at the spine in AS- ≥ 4 years.

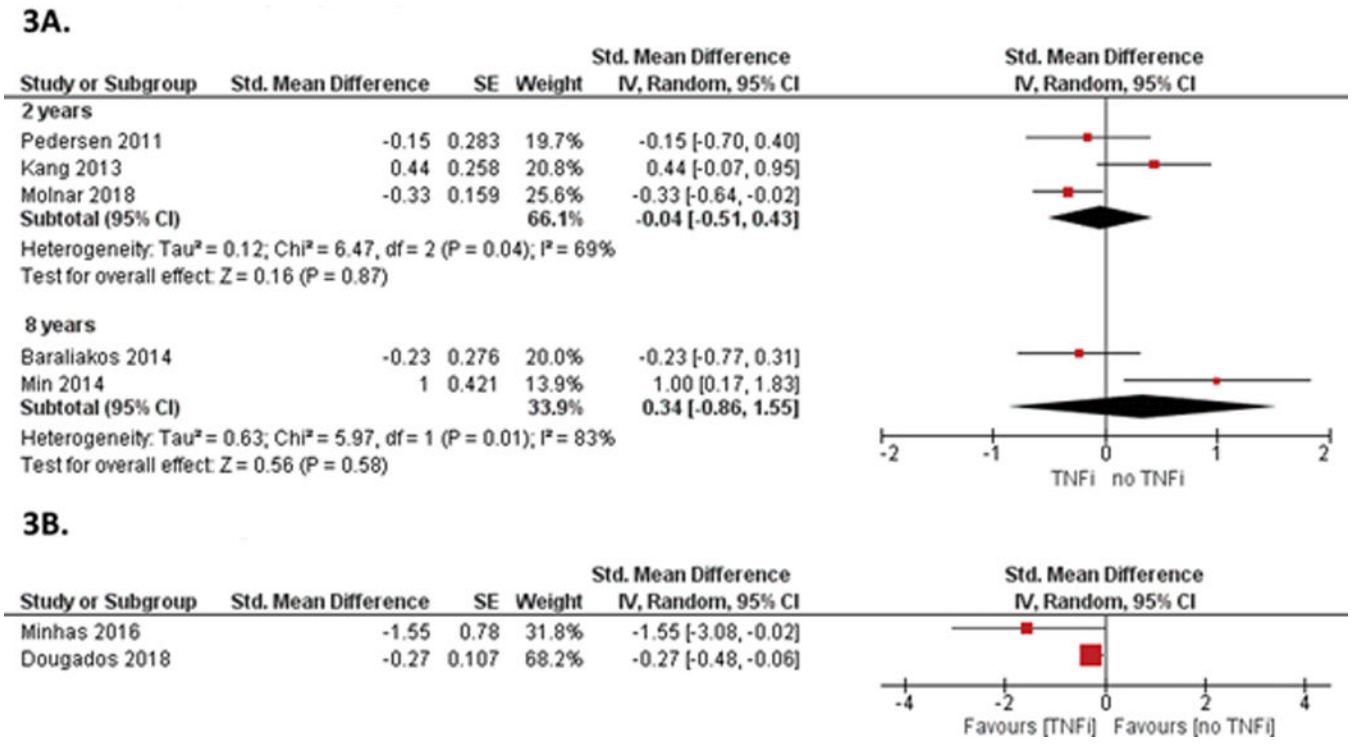

Figure 3.

Forest plot of radiographic progression in patients on tumor necrosis factor inhibitor alpha (TNFi) A) change in the number of syndesmophytes, and B) radiographic progression at sacroiliac joint (SIJ) in AS and nr-axSpA respectively.

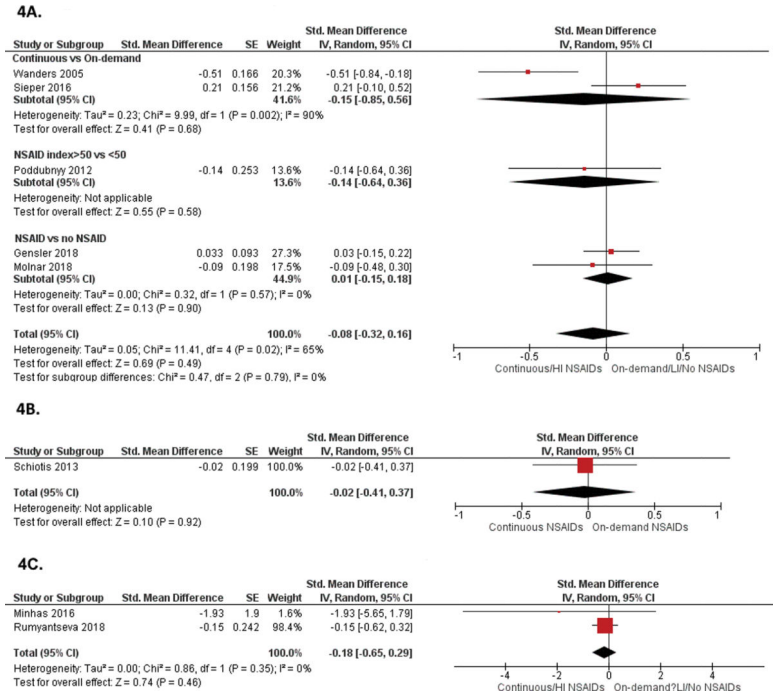

Figure 4.

Forest plot of radiographic progression in patients on non-steroidal anti-inflammatory drugs (NSAIDs) A) radiographic progression at the spine in AS at 2 years (mSASSS only), B) radiographic progression at the spine in AS at 3 years (BASRI-spine), and C) radiographic progression at SIJ in AS and early axSpA respectively.

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Table 1.

Baseline characteristics of the included studies

Author, Year	Study Design	Follow-up duration (years)	AS/ AxSpA characteristics	Treatment				Control			
				Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)	Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)
TNFi											
Baraliakos 2005 [42]	Open label extension of RCT	2	Active AS	Infliximab 5 mg/kg IV every 6 wk	41	15.5 (7.5)	12.1 (16.9)	No TNFi, GESPIC historical cohort	41	5.5 (2.25)	5.9 (13.4)
Baraliakos 2007 [22]	Open label extension of RCT	4	Active AS (same cohort as 2005 study)	Infliximab 5 mg/kg IV every 6 wk	33	19.0 (23.4)	11.6 (15.3)	No TNFi, OASIS historical cohort	132	11.7 (9.3)	12.7 (17.4)
van der Heijde (I) 2008 [24]	Open label extension of 24 week RCT	2 (96 wk)	Active AS (ASSERT cohort)	Infliximab 5 mg/kg IV every 6 wk after loading dose	201	10.2 (8.7)	17.7 (17.9)	No TNFi, OASIS historical cohort-matched	70	9.9 (8.8)	17.5 (19.1)
van der Heijde (E) 2008 [23]	Open label extension of 24 week RCT	2 (96 wk)	AS	Etanercept 25 mg SC twice a wk	257	10 (8.5)	14 (17.6)	No TNFi, OASIS historical cohort (meeting RCT entry criteria)	76	12 (9.8)	19 (20.8)
van der Heijde 2009 [21]	Open label extension of 24 week RCT	2	AS (Canadian [M03–606] study and the ATLAS study group	Adalimumab 40 mg SC every other week	307	19.8 (19.3)	19.8 (19.3)	No TNFi, OASIS historical cohort (eligible patients)	77	11.3 (8.7)	15.8 (17.6)
Pedersen 2011 [45]	Cohort study	2	AS	Infliximab 3 or 5 mg/kg (11), etanercept 25 mg twice a wk (10), adalimumab 40 mg every other wk (2)	23	18.2 (11.4)	14.5 916.1)	No TNFi, standard therapy	27	15 (10)	10.0 (12.1)
Haroon 2013 [27]	Cohort, prospective	1.5 to 9	AS	TNFi- type and dose not specified	201	-	-	No TNFi	133	-	-
Kang 2013 [46]	Cohort study	2	AS	Infliximab, etanercept or adalimumab	26	9.5 (5.1)	4.0 (6.6)	No TNFi (NSAID and/or MTX or SSZ)	37	8.0 (4.5)	3.7 (6.8)

Author, Year	Study Design	Follow-up duration (years)	AS/ AxSpA characteristics	Treatment				Control			
				Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)	Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)
Min 2014 [38]	Cohort, retrospective, single-center	8	AS	TNFi- type and dose not specified	14	-	-	Continuous NSAIDs	12	-	-
Braun 2014 [35]	Phase 3, multicentric, randomized, placebo-controlled, double- blind, placebo crossover	2 (104 wk)	Active AS (GO-RAISE trial)	Golimumab 50 or 100 mg every 4 wk	233	7.25 (35.59)	12.64 (17.71)	Placebo, crossover to golimumab 50 mg at wk 16 or 24	66	5.20 (45.94)	16.1 (18.7)
		4	Active AS (GO-RAISE trial)	Golimumab 50 or 100 mg every 4 wk	233	7.25 (35.59)	12.64 (17.71)	Placebo, crossover to golimumab 50 mg at wk 16 or 24	66	5.20 (45.94)	16.1 (18.7)
Baraliakos 2014 [43]	Open label extension of RCT	8	AS (DIKAS)	Infliximab 5 mg/kg IV every 6 wk	22	15.8 (8.5)	13.2 (17.6)- adjusted to 13.8 for comparison	No TNFi, Herne historical cohort	34	20.7 (5.7)	14.2 (13.8)- adjusted to 13.8 for comparison
Chung 2015 [47]	Clinical trial	4 (42– 66 mo)	AS	TNFi- type and dose not specified	25	4.15 (4.02)	-	No TNFi	25	2.13 (1.73)	-
Minhas 2016 [25]	Cohort, prospective	≥2, up to >10 (Median= 3)	AS (PSOAS cohort)	TNFi (>50% of FU)- type and dose not specified	630 (total)	-	-	No TNFi (<50% of FU period)	630 (total)	-	-
Kim 2016 [48]	Cohort, prospective	5	AS (OKSAR cohort)	TNFi- type and dose not specified	269	11.33 (7.51)	18.87 (17.96)	TNF naïve	341	8.04 (6.57)	15.68 (15.49)
Dougados 2018 [41]	Open label extension of RCT	2	Nr-axSpA (EMBARK trial)	Etanercept 25 mg SC twice a wk	162	2.4 (1.8)	Baseline total SIJ score- 1.5 (1.2)	No biologics, Contemporary DESIR cohort	193	1.70 (1.0)	Baseline SIJ score= 1.9 (1.6)
Molnar 2018 [34]	Cohort study	10 (2 year radiographic interval progression)	AS (patients fulfilling modified NY criteria for AS from SCQM AxSpA cohort)	Any TNFi before radiographic interval, NSAIDs	163	13.8 (9.7)	6.6 (12.5)	No TNFi before radiographic interval	269	-	-
Gensler 2018 [26]	Cohort, prospective	2, 4	AS (PSOAS cohort)	TNFi- type and dose not specified	239	16.8 (12.5)	14.2 (19.6)	No TNFi	280	16.8 (12.5)	14.2 (19.6)
Park 2019 [44]	Cohort study, single center	4	Early AS (<10 year symptom duration)	TNFi- type and dose not specified	135	2.7 (2.6)	6.2 (9.9)	NSAIDs, Control group from different institution	80	0.7 (1.8)	7.3 (10.8)

Author, Year	Study Design	Follow-up duration (years)	AS/ AxSpA characteristics	Treatment				Control			
				Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)	Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)
								(same location-Seoul)			
NSAIDs											
Wanders 2005 [37]	RCT, open label, radiographs blinded	2	AS patients	Continuous NSAIDs (started on celecoxib 200 mg bid but allowed to increase or change NSAID)	76	13 (10.2)	7.9 (14.7)	On-demand NSAIDs (celecoxib or another NSAID)	74	10.2 (9.3)	9.3 (15.2)
Poddubnyy 2012 [49]	Cohort study	2	AxSpA (GESPIC)	High NSAID intake (NSAID intake ≥50)	43	-	-	Low NSAID intake (NSAID index <50)	121	-	-
			AS		24	5.5 (2.7)	6.7 (7.7)		64	5.0 (2.9)	5.7 (11.6)
			Nr-AxSpA		19	3.7 (2.1)	1.6 (4.0)		57	3.0 (2.2)	2.6 (4.8)
Gensler 2018 [26]	Cohort, prospective	2,4	AS (PSOAS cohort)	NSAIDs	343	16.8 (12.5)	14.2 (19.6)	No NSAIDs	176	16.8 (12.5)	14.2 (19.6)
Schiotis 2013 [50]	Cohort study	3	AS (REGISPONSER), BASRI spine ≥12 excluded	Continuous NSAIDs	81	25.32 (9.38)	BASRI spine- 7.23 (3.34)	On-demand NSAIDs	37	25.54 (12.3)	BASRI-spine= 6.69 (3.4)
Minhas 2016 [25]	Cohort, prospective	>2, up to >10 (Median= 3)	AS (PSOAS cohort)	NSAID index>50	total in both groups=630	-	-	-	total in both groups=630	-	-
Sieper 2016 [36]	RCT, open label, radiographs blinded	2	AS (ENRADAS)	Continuous Diclofenac 150 mg /day (or equivalent dose if could not tolerate)	85	12.2 (10.3)	11.3 (14.9)	On-demand NSAIDs	82	15.2 (12.4)	14.0 (16.8)
Molnar 2018 [34]	Cohort study	10 (2 year radiographic interval progression)	AS (patients fulfilling modified NY criteria for AS from SCQM AxSpA cohort)	NSAIDs	286	13.8 (9.7)	6.6 (12.5)	no NSAIDs	55	-	-
Rumyantseva 2018 [39]	Cohort study	2	Early AxSpA	Continuous NSAIDs	35	24.1 (15.4)	SIJ score- 3.67 (0.74)	On-demand NSAIDs	33	24.1 (15.4)	3 (1.48)
Secukinumab											

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Author, Year	Study Design	Follow-up duration (years)	AS/ AxSpA characteristics	Treatment				Control			
				Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)	Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)
Braun 2018 [51]	Retrospective analysis of RCT	2	AS (MEASURE 1)	Secukinumab 150 mg or 75 mg IV every 4 wk	168	-	9.55 (14.14)	Biologic-naïve (on NSAIDs only), ENRADAS	69	-	9.95 (13.76)

AS- ankylosing spondylitis (defined as meeting modified New York criteria), axSpA- axial spondyloarthritis, nr- non-radiographic, N- number of participants, wk-week, SD- standard deviation, mSASSS- modified Stoke AS Spine Score, TNFi- tumor necrosis factor alpha, NSAIDs- non-steroidal anti-inflammatory drugs, BASRI(Bath AS Radiology Index), SIJ- sacroiliac joint, OASIS -Outcome Assessment in Ankylosing Spondylitis, ASSERT-Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy, ATLAS- Adalimumab Trial Evaluating Long-term Efficacy and Safety for Ankylosing Spondylitis, SCQM- Swiss Clinical Quality Management, GESPIC- early German AS cohort, DIKAS- Seutsche Infliximab Kohorte fur AS, GO-RAISE- golimumab in ankylosing spondylitis, PSOAS- Prospective Study of Outcomes in Ankylosing Spondylitis, GLAS- Groningen Leeuwarden AS, ENRADAS- Effects of NSAIDs on Radiographic Damage in Ankylosing Spondylitis, DESIR- French Cohort of Undifferentiated Spondyloarthritis, REGISPONSER- Spanish National Registry of Spondyloarthropathies.

Table 2.

Radiographic progression at the spine and sacroiliac joint in the included studies

Author, Year	Follow-up duration (years)	Treatment			Control			Difference between groups
		N	Change in mSASSS (SD)	No of new syndesmophytes (SD), other radiographic parameters	N	Change in mSASSS (SD)	No of new syndesmophytes (SD), other radiographic parameters	
TNFi								
Baraliakos 2005 **[42]**	2	41	0.4 (2.7)	-	41	0.7 (2.8)	-	-
Baraliakos 2007 **[22]**	4	33	1.6 (2.6)	-	132	4.4 (26.21)	-	-
van der Heijde (I) 2008 **[24]**	2	201	0.9 (2.6)	-	70	1.2 (3.9)	-	-
van der Heijde (E) 2008 **[23]**	2	257	0.91 (2.45)	Change in Cervical radiography score- 0.49 (1.40), Lumbar radiography score- 0.42 (1.84)	76	1.27 (3.64)	Change in Cervical radiography score- 0.53 (2.29), Lumbar radiography score- 0.73 (2.00)	-
van der Heijde 2009 **[21]**	2	307	0.8 (2.6)	-	77	0.9 (4.1)	-	-
Pedersen 2011 **[45]**	2	23	1.4 (1.9)	0.52 (0.8)	27	1.5 (3.1)	0.70 (1.4)	-
Haroon 2013 **[27]**	>1.5 to 9	201	-	-	133	-	-	mSASSS OR- 0.52 (0.30 to 0.88)
Kang 2013 **[46]**	2	26	3.3 (4.2)	0.9 (1.4)	37	2.3 (5.1)	0.4 (0.9)	-
Min 2014 **[38]**	8	14	9.29 (6.22)	2.79 (2.94)	12	4.58 (2.15)	0.50 (0.674)	-
Braun 2014 **[35]**	2	233	0.9 (3.33)	-	66	1.6 (4.6)	-	-
	4	233	1.67 (4.89)	-	66	2.1 (5.2)	-	-
Baraliakos 2014 **[43]**	2	22	3.2 (7.04)	-	34	2.7 (9.33)	-	-
	4		4.4 (6.57)	-	-	17.5 (10.49)	-	-
	6		6.2 (6.57)	-	-	19.3 (7.58)	-	-
	8		7.2 (6.57)	1 (8.64)	-	11.70 (6.41)	2.70 (6.25)	-
Chung 2015 **[47]**	4	25	-	Change in CT score of facet joints, total spine- 11.72 (53.94)	25	-	Change in CT score of facet joints, total spine- 11.56 (43.02)	-
Minhas 2016 **[25]**	>2, up to >10	630	-	-	-	-	-	BASRI (radiographic change in SI joint) OR- 0.06 (0.004 to 0.99)
Kim 2016 **[48]**	5	269	4.73 (18.56)	-	341	6.14 (32.80)	-	-

Author, Year	Follow-up duration (years)	Treatment			Control			Difference between groups
		N	Change in mSASSS (SD)	No of new syndesmophytes (SD), other radiographic parameters	N	Change in mSASSS (SD)	No of new syndesmophytes (SD), other radiographic parameters	
Dougados 2018 **[41]**	2	162	-	Change in total SIJ score= −0.14 (0.81)	193	-	Change in total SIJ score= 0.08 (0.83)	-0.22 (95% CI −0.38,−0.06)
Molnar 2018 **[34]**	10 (2 year radiographic interval progression)	163	-	-	269	-	-	mSASSS OR- 0.50 (95% CI 0.28 to 0.88), progression of ≥1 new syndesmophytes per 2 years- OR 0.55 (0.33 to 0.94)
Gensler 2018 **[26]**	2	239	-	-	280	-	-	Mean mSASSS difference= −0.71 (−2.10 to 0.68, p=0.32)
	4	239	-	-	280	-	-	Mean mSASSS difference= −1.37 (−2.07 to −0.63 p<0.001)
Park 2019 **[44]**	4	135	-	-	80	-	-	OR - 0.41 (95% CI 0.22 to 0.75)
NSAIDs								
Wanders 2005 **[37]**	2	76	0.4 (1.7)	-	74	1.5 (2.5)	-	-
Poddubnyy 2012 **[49]**	2	43		-			-	-
	AS	24	0.02 (1.39)	-	64	0.96 (2.78)	-	-
	Nr-axSpA	19	0.51 (1.72)	-	57	0.74 (1.95)	-	-
Gensler 2018 **[26]**	2	343	-	-	176	-	-	Mean mSASSS difference= 0.64 (−1.52 to 2.81, p=0.56)
	4	343	-	-	176	-	-	Mean mSASSS difference= 1.95 (0.90 to 2.99, p <0.001)
Schiotis 2013 **[50]**	3	81	-	Change in BASRI spine- 0.64 (1.22)	37	-	Change in BASRI spine- 0.66 (1.04)	-
Minhas 2016 **[25]**	>2, up to >10	630	-	-		-	-	BASRI SIJ OR- 0.03 (0.002 to 3.50)
Sieper 2016 **[36]**	2	85	1.29 (2.82)	-	82	0.71 (2.77)	-	-
Molnar 2018 **[34]**	10 (2 year radiographic interval progression)	286	-	-	55	-	-	OR- 0.85 (0.42 to 1.72), progression of ≥1 new syndesmophytes per 2 years- OR 1.04 (0.50 to 2.17)
Rumyantseva 2018 **[39]**	2	35	-	Change in SIJ score= 1 (1.66)	33	-	Change in SIJ score-=1.33 (2.67)	-
Secukinumab								

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Author, Year	Follow-up duration (years)	Treatment			Control			Difference between groups
		N	Change in mSASSS (SD)	No of new syndesmophytes (SD), other radiographic parameters	N	Change in mSASSS (SD)	No of new syndesmophytes (SD), other radiographic parameters	
Braun 2018 **[51]**	2	168	0.55 (1.82)	% with no radiographic progression 61%	69	0.89 (1.83)	% with no radiographic progression 52%	-

AS- ankylosing spondylitis, Nr-axSpA- non-radiographic axial spondyloarthritis, N- number of participants, SD- standard deviation, mSASSS- modified Stoke AS Spine Score, TNFi- tumor necrosis factor alpha, NSAIDs- non-steroidal anti-inflammatory drugs, BASRI- Bath AS Radiology Index-spine, SIJ- sacroiliac joint, CT- computed tomography.