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Efficacy and Safety of Janus Kinase Inhibitors (JAKi) versus Interleukin 17 Inhibitors (IL-17i) in the Treatment of Active Non-Radiographic Axial Spondyloarthritis (nr-ax SpA), a Comparative Systematized Review

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Abstract

Background: Non-radiographic axial spondyloarthritis is a progressive and disabling inflammatory disease affecting young adults, with limited treatment options. TNFi are more efficacious than JAKi and IL1-7i in nr-ax SPA and it has a well-known safety profile over a longer duration. Recently, many IL-17i and JAKi were approved for the treatment of nr-ax SPA; however, data comparing IL1-7i and JAKi in terms of efficacy and safety is lacking. This systematized review aimed to compare the existing efficacy and safety data of JAKi vs IL-17i in the treatment of patients with nr-ax SPA. **Methods:** A systematic literature search was performed using relevant keywords in many databases. According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA, 2020), relevant articles were included and evaluated in this review. Efficacy and safety data were collected, analyzed and compared through week 52. The first check was done by the end of week 14 and week 16 for upadacitinib and IL-17i respectively. **Results:** Data from four RCTs evaluating upadacitinib, secukinumab, ixekizumab, and bimekizumab comprising 1425 patients were analyzed. Overall, a comparable efficacy and safety profile were observed across different treatment arms through week 52; however, non-significant variations were encountered in some outcome measures. The primary endpoint among these RCTs (ASAS40 response rate) was met and it was higher in patients treated with bimekizumab 160 mg sc Q 4 weeks in TNFi non responders (48%) and lowest in ixekizumab 80 mg sc Q 4 weeks treated patients, (35%) ($p < 0.05$, 95% CI). **Conclusion:** The above-mentioned three

IL-17i and the only one JAKi demonstrated comparable safety and efficacy profiles with some minor variations. A head-to-head trial comparing the effectiveness and safety characteristics of JAKi vs IL-17i may be needed in patients with active nr-ax SpA.

Keywords

Non-Radiographic Axial Spondyloarthritis, nr-ax SPA, JAKi, Interleukin 17 Inhibitors, IL-17i, Janus Kinase Inhibitors

1. Introduction

Spondyloarthritis (SpA) also known as spondyloarthropathy, is a group of inflammatory joints diseases that tend to involve axial joints, particularly sacroiliac joints. It may involve peripheral joints in different patterns in addition to enthesis along with variable extra-articular features. Five major subtypes of SpA are recognized according to the classification criteria proposed by the Assessment of Spondyloarthritis International Society (ASAS) classification criteria and the European Spondyloarthropathy Study Group (ESSG). These are: Ankylosing Spondylitis (AS), Reactive Arthritis (ReA), Psoriatic Arthritis (PsA), Enteropathic Arthritis (EA) associated with inflammatory bowel disease (IBD), and Undifferentiated Spondyloarthritis (uSpA), [1].

Depending on the presence or absence of radiographic changes on sacroiliac joints, axial SPA is further sub-classified into radiographic (formerly ankylosing spondylitis) and non-radiographic SPA (nr-ax SpA). The latter could represent early AS or encountered in psoriatic, reactive, enteropathic and undifferentiated SpA, [2].

The estimated prevalence of ax SpA and its subtypes is variable worldwide and its comparison was limited by discrepancies in methodologies. In addition, most of the epidemiological data predated the development of the ASAS criteria for ax SpA; hence, it was related to AS rather than nr-ax SpA, [3]. The estimated proportion of patients with nr-ax SPA among all patients with axial spondyloarthritis is 40% - 60%, [4]. The prevalence of nr-ax SpA is slightly higher in women, and white than in men and black population. Axial SPA commonly affects young adults during their work-productive age and has a significant impact on quality of life, either because of associated chronic symptoms (pain, stiffness and fatigue), or because of resultant disabilities. Male gender, elevated CRP, activity features in MRI of SIJs and HLA-B27 positivity are proven predictors for radiographic progression as well as better response to treatment, [5].

The exact etiology and pathogenesis of spondyloarthritis are still not well understood; however, a complex interaction of genetics, microbiomes, environmental factors and biomechanics does exist, [6]. HLA-B27 is positive in 80% - 90% of patients with axial SPA in general, whereas its frequency among the general

population is less than 10%; even though, the risk of developing ax-SPA is as high as 5% - 7% in HLA-B27-positive individuals, [7]. The inflammation normally starts in the sacroiliac joints (SIJs), but later can extend to inflammatory and structural changes in the spine. Chronic active axial inflammation presents clinically with axial pain, stiffness, and limited mobility. If not properly treated, structural damages such as erosion, subchondral sclerosis, joint space narrowing and axial ankylosis do occur resulting in marked functional impairment and poor quality of life. Such structural damage was found to be slowly progressing over 2 - 10 years in some cohorts, [8].

Magnetic resonance image (MRI) has become an invaluable tool in early diagnosis as it can detect active inflammation in the spine and sacroiliac joints (SIJs) that is not visible on plain radiography. Sacroiliitis can be detected by MRI years before it is apparent on a plain radiograph, nevertheless, a negative MRI of the SIJs does not exclude SpA. Even in patients with nr-ax SpA, the T1-weighted (T1W) sequence detects signal from fat, so adult bone marrow of iliac and sacral bones is bright due to its fat content. When the signal from fat suppressed using fat-suppressed sequences such as short tau inversion recovery (STIR), the active inflammation in the bone marrow would be visualized. Furthermore, several structural lesions could be observed such as erosions and ankylosis, [9].

In clinical rheumatology practice, the inflammatory markers CRP and ESR are frequently used to aid in the diagnosis and monitoring for treatment responses of different autoimmune rheumatic diseases. Unfortunately, due to their low sensitivity and specificity, they may not fully represent the inflammatory process in ax SpA; however, high level of CRP is one of the items included in the classification criteria of the ASAS for ax SpA. Although elevated CRP or ESR levels are detected only in 40% - 50% of patients with AS, and the degree of inflammation fluctuates in patients with ax SpA, they correlate well with the BASDAI and MRI score.

The optimal management of nr-ax SPA depends on accurate early diagnosis and treatment. The treatment of ax SpA involves non-pharmacological and pharmacological treatment aiming to achieve remission or low disease activity. For a long time, the only available treatment for AS were non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. In the last two decades, tumor necrosis factor alpha inhibitors (TNFi) and other biological agents were introduced and revolutionized the treatment of ax SPA, and many other auto-immune mediated disorders.

In this review, we focused on IL-17i and JAKi in the treatment of nr-ax SPA and we compared its safety and efficacy as indicated by different response criteria.

2. Methodology

2.1. Data Collection

A systematic literature search was performed using relevant keywords in many databases such as Cochrane, PubMed, Embase, and clinical trial.gov databases. The key words were non-radiographic axial spondyloarthritis, nr-ax SPA, JAK

inhibitors, JAKi, interleukin 17 inhibitors, IL-17i, and Janus kinase inhibitors. Techniques such as citation tracking and following similar or "related to" articles were also applied to capture more and more articles.

Inclusion criteria:

- All articles that had evaluated IL-17i or JAKi in axial SPA between 2004-2024 regardless of the country, population, language of publication or the status of access.

Exclusion criteria:

- Articles that purely addressed radiographic ax SPA (AS)
- Articles without available full text
- Duplicated data
- Case reports, case series, and systematic reviews

According to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), 2020 updated version, [10] see **Figure 1**. Four randomized control trials assessing the efficacy and safety of JAKi and IL 17i in patients with active nr-ax SPA were selected, evaluated and summarized in this review. These were: SELECT-AXIS 2, PREVENT, COAST-X and BEMOBILE 1 trials. The targeted population in all these four trials were adults aged ≥ 18 years who met the ASAS classification criteria for non-radiographic axial spondyloarthritis. Additionally, they have an active disease as defined by a clinical activity index in addition to objective evidence of disease activity, either elevated C-reactive protein (CRP) or MRI of SIJs/spine.

The primary end point was ASAS40 response rate across all these four RCTs, however, many other secondary endpoints and adverse events were reported in each trial. These measures were assessed at baseline (week 0) and reassessed at week 14 for upadacitinib, at week 16 for IL-17i, and once again at week 52 for all. Secondary endpoints including different activity indices, physical functions and quality of life measures were encountered variably among the included trials. The encountered physical functions parameters include change from Baseline (CfB) in Ankylosing spondylitis Quality of Life (ASQoL), Bath Ankylosing Spondylitis Functional Index (BASFI), and Total and Nocturnal Spinal Pain. Similarly, we looked at the changes of the objective signs of inflammation; high sensitivity CRP and MRI SIJs scores such as Spondyloarthritis Research Consortium of Canada, (SPARCC). The BASFI and ASQoL were only assessed in SELECT AXIS2 and BEMOBILE1 at the first check point. Similarly, ASAS LDA, ASAS ID, ASAS PR BASDI 50, pain, physical function and hs-CRP were encountered through 52 only in both these trials. That is why we compared these measures in upadacitinib (JAKi) treated patients versus bimekizumab as an IL-17i representative.

For the definitions of different outcome measures including the primary end point, see (**Appendix 1**).

2.2. Data Management and Statistical Analysis

The collected data was extracted and organized in a structured excel data sheet.

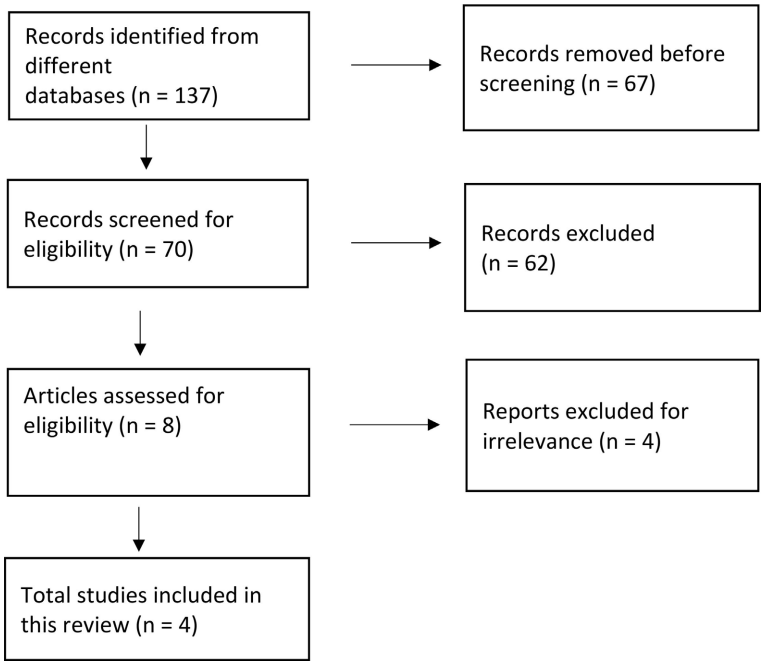

Figure 1. The PRISMA flow diagram JAKi and IL-17i in nr ax-SPA.

Different outcome measures were evaluated including disease activity measures, functional and quality of life measures. We looked at every single measure in each trial at the two check points and the response rate/outcome for that measure was recorded.

Similar outcomes measures among these trials were summarized in tables and represented in excel graphs to be easily compared. To minimize errors and for quality purposes, all the collected data were rechecked before data analysis.

A simple comparison was made between the primary end point (the ASAS40) response rates among all these four trials and represented in graphs. Similarly, other secondary endpoints records were compared and displayed in graphs.

3. Results

Four RCTs comprising a total of 1425 patients were found to be eligible and included in this systematized review. They were: SELECT-AXIS2, PREVENT, COAST-X, and BEMOBILE1; which evaluated the efficacy and safety of upadacitinib, secukinumab, ixekizumab, and bimekizumab in patients with active nr-ax SpA, respectively. The above mentioned 4 studies were multi-center, randomized, double-blind, placebo-controlled, phase 3 trials conducted across many countries mainly in Europe, Asia, Australia, North America, and South America, see **Table 1** for more details.

The mean age of patients in was comparable among these RCTs: 42 years in SELECT-AXIS 2 study, 39.5 years in PREVENT trial, 40.5 years in COAST-X, and 39.5 years in BEMOBILE1 (mean ± SD 11 - 12 years). At baseline, most patients were female in three of these four study, 183 of 313 patients, (59%) in SELECT-AXIS 2, 300 of 555 patients (54.1%) in PREVENT trial and 160 of 303 patients,

Table 1. Summary of the included 4 Randomized Control Trials, RCTs.

STUDY	Registration Number at clinicaltrial.gov & doi	Drug vs PCB	Distribution	Total n at wk 16	n&% at wk 52
SELECT AXIX 2 (Deodhar *et al.*, 2022) (113 sites in 23 countries)	**NCT04169373** Doi: 10.1136/annrheumdis-2022-eular.2534.	Upadacitinib 15 mg od	**157**	**313**	**259 (82.7%)**
		PCB	**156**		
PREVENT ((Deodhar *et al.*, 2021) **(130 sites in 24 countries)**	**NCT02696031** Doi: 10.1002/art.41477	Secukinumab 150 LD	**185**	**555**	**481 (86.6 %)**
		Secukinumab 150 NL	**184**		
		PCB	**186**		
COAST-X (Deodhar *et al.*, 2020) **(107 sites in 15 countries)**	**NCT02757352** Doi: 10.1016/S0140-6736(19)32971-X	Ixekizumab 80 MG SC Q4W	**96**	**303**	**265 (87.4%)**
		Ixekizumab 80 MG SC Q2W	**102**		
		PCB	**105**		
BE MOBILE 1 (Baraliakos *et al.*, 2023)**(83 sites in 13 countries)**	**NCT03928704** Doi: 10.1136/ard-2023-224803	Bimekizumab 160 mg Q4W	**128**	**254**	**220 (86.6%)**
		PCB	**126**		

(53%) in COAST-X trial. However, in BEMOBILE1 most patients were males 138 of 254 patients (54%). Most patients were HLA-B27 positive (59%) in SELECT trial, 69% (382/555) in PREVENT, around 74% in COAST-X, and 197 of 254 patients (77.6%) in BEMOBILE1.

Similarly, most patient have had an elevated high sensitivity C- reactive protein and/or an MRI evident active sacroiliitis across all trials. Background treatments were comparable in upadacitinib and bimekizumab group representing JAKi and IL = 17i. For instance, in SELECT-AXIS2, most patients (75%) used concomitant therapy with NSAIDs followed by conventional synthetic DMARDs (29%) and oral corticosteroids (11%) at baseline compared to (74%), (24%) and (8%) in BEMOBILE1 respectively. However, 34% of patients in SELECT-AXIS2 had previous bDMARDs exposure compared to 11% in BEMOBILE1.

3.1. Efficacy Data at Week 14 for JAKi and Week 16 for IL17i

3.1.1. The Primary end Point, ASAS40

The ASAS40 response rate was significantly higher in patients treated with bimekizumab 160 mg sc Q4wks in TNFi non responders imputation (NRI), (48%) and TNFi naïve (47%) followed by upadacitinib 15 mg PO OD (45%, $p < 0.001$), secukinumab 150 mg NL (41%), secukinumab 150 mg LD (41%), ixekizumab 80 mg sc Q2weeks, (40%), and ixekizumab 80 mg SC Q4weeks (35%), (p value < 0.05, 95 % CI), see Figure 2. Note, patients in the upadacitinib group had achieved the ASAS40 from week 2 compared to as early as week 1 in ixekizumab and bimekizumab groups.

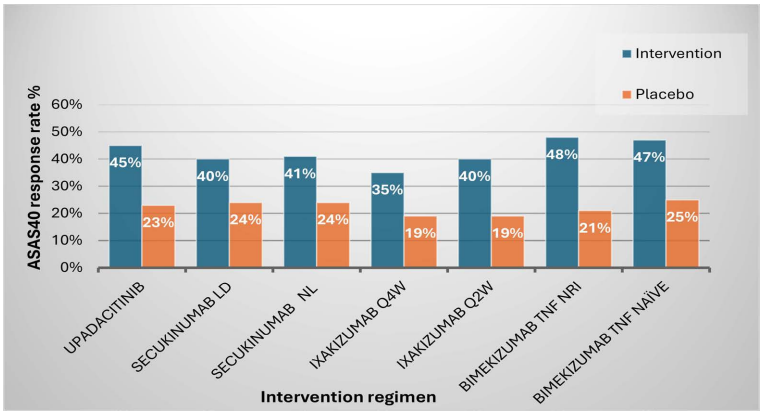

Figure 2. ASAS40 response rates, intervention versus placebo.

3.1.2. ASAS PR Response Rates

The ASAS PR was highest among patients who received IL17i, BMZ (26%, $p < 0.001$), secukinumab LD (22%), and secukinumab NL (21%) compared to upadacitinib treated patients (19%), (p value < 0.05, 95 % CI), see **Figure 3**.

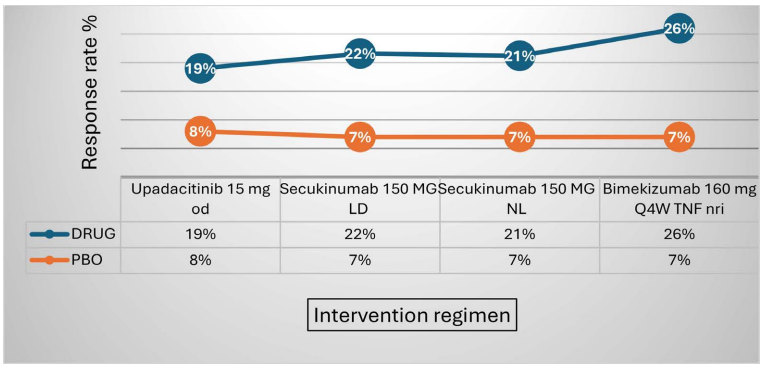

Figure 3. ASAS PR response rates, intervention versus placebo.

3.1.3. BASDAI50 Response Rates

Similarly, BASDAI50 response rate was highest in patients who received BMZ (47%), upadacitinib (42%), secukinumab NL (38%) and lowest in SEC LD (37%), (p value < 0.05, 95 % CI), see **Figure 4**.

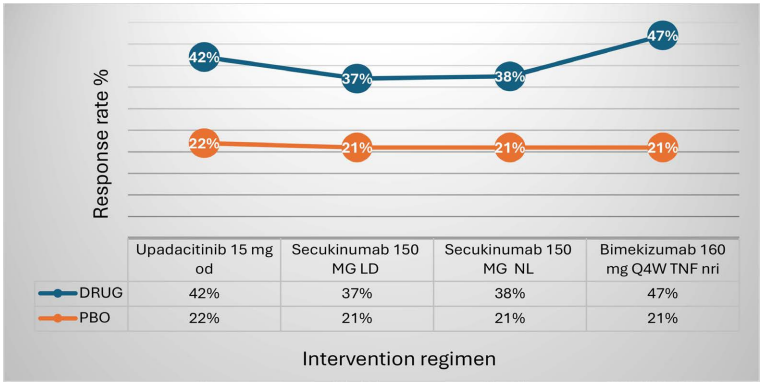

Figure 4. BASDAI50 response rates, intervention versus placebo.

3.1.4. ASDAS CRP ID Response Rates

The ASDAS CRP ID response rate was highest in those who received JAKi at week 14 (45%, $p < 0.05$) and lowest in IL-17i treated patients, around (16%) in secukinumab NL, see Figure 5.

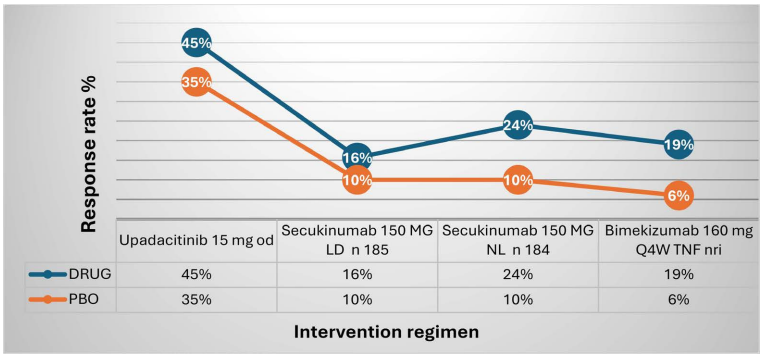

Figure 5. ASDAS-CRP ID response rates, intervention versus placebo.

3.1.5. ASAS20 Response Rates

The ASAS 20 response rate was comparable between patients treated with upadacitinib (67%) and bimekizumab TNF NRI patients (69%) respectively; however, it was lower in patients treated with secukinumab (57%) and lowest in bimekizumab-TNF naïve patients (47%), (p value < 0.05, 95 % CI), see Figure 6.

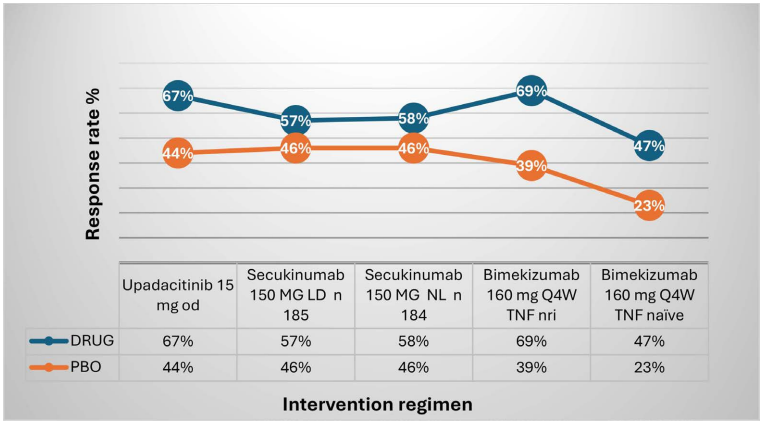

Figure 6. ASAS20 response rates, intervention versus placebo.

3.1.6. Other Outcomes Measures

Other secondary endpoints such as ASQoL, BASFI, total and nocturnal spinal pain were similarly encountered in SELECT AXIS-2 and BEMOBILE1 trials; hence, these outcomes were compared in patients treated with upadacitinib and bimekizumab along with the objective signs of inflammation (hs CRP, MRI SIJs, and MRI spine). Statistically significant improvements were achieved in most of these secondary endpoints in both of intervention drugs and its corresponding placebo. In terms of improvement from base line, both agents demonstrated a significant and comparable improvement in ASQoL, (−5.3) and (−5.2), respectively. Likewise, a comparable improvement was achieved in BASFI, total spinal

pain and nocturnal spinal pain, see Figure 7.

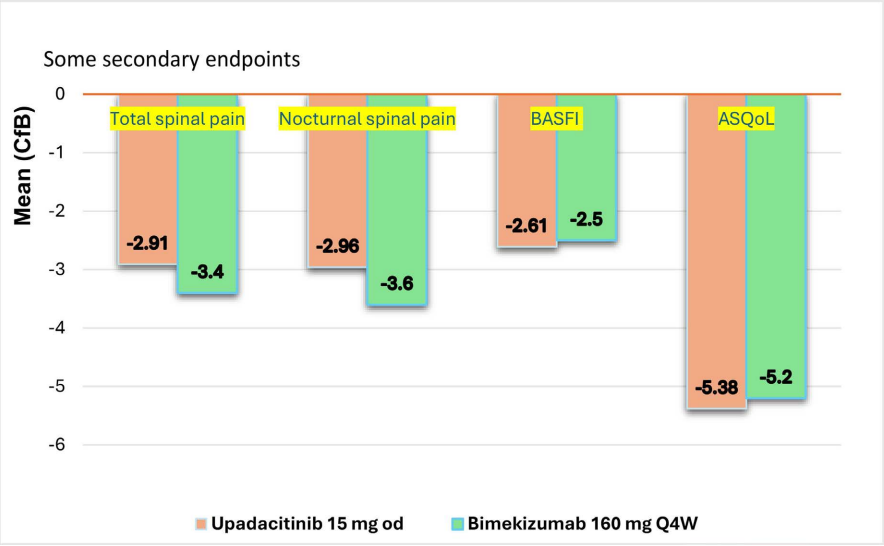

Figure 7. Upadacitinib at wk14 vs bimekizumab at week 16 in some secondary endpoints.

Improvements from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) in patients with baseline enthesitis were not statistically significant in upadacitinib treated patients compared with the placebo group at week 14. Similarly, in bimekizumab treated patients, change from baseline in BASMI were not statistically significant.

Objective signs of inflammation:

Objective signs of inflammation such as, high sensitivity CRP, SPARCC MRI sacroiliac joint scores and spine were evaluated at screening and at week 14 for upadacitinib treated patients and at week 16 for IL-17 inhibitors; thus, changes from baseline in these measures were recorded.

3.1.7. High Sensitivity CRP (hs-CRP)

Reduction in hs-CRP was observed at the first checkpoint (week 14 or 16) in all treatment groups including JAKi and IL-17i. It is worth emphasizing that hs CRP as well as active sacroiliitis on MRI SIJs are predictors for better response to treatment and this was evident by the achievement of ASAS40 in those who have a higher hs CRP level and a higher activity index on MRI. For instance, in secukinumab treated patients, the ASAS40 response rate at week 16 was 52.3% in the overall population who were CRP positive & MRI positive at screening. In comparison to the other two subgroups, it was 36.8% among patients with negative CRP & positive MRI and 33.0% among those with positive CRP and negative MRI. Furthermore, this was also observed in other outcome measures other than ASAS40 such as: ASAS PR, ASDAS - CRP ID, BASDAI and BASFI scores.

3.1.8. MRI SIJs

In SELECT AXIS2 trial, MRI scans of sacroiliac joints and spine were performed

at baseline and week 14; a final MRI scan was planned at week 104 and no MRI scans were done at week 52. In BEMOBILE1, MRI evaluation was done at baseline and at week 52. Therefore, MRI findings in patients treated with upadacitinib versus IL-17i were compared only at week 14 vs 16 respectively. It is worth mentioning that MRI SPARCC SIJ inflammation scores range from 0 to 72; lower scores indicate less SIJ inflammation and negative changes represent improvements. Improvement was measured by mean change from baseline (CfB) in SPARCC MRI sacroiliac joint score.

MRI findings indicating active disease in the sacroiliac joints (sacroiliitis) include juxta-articular bone marrow oedema and contrast enhancement of the bone marrow. In the upadacitinib treated patients, the SPARCC MRI sacroiliac joint score was −2.49 at week 14 compared to −6.2 improvement in bimekizumab and −4.52 in ixekizumab Q2 weeks at week 16. So, two IL-17i demonstrated better improvement than the JAKi in SPARCC MRI sacroiliac joint score after 3 - 4 months of treatment. Nevertheless, patients in secukinumab NL arm achieved the lowest improvement, (−1.03), see Figure 8.

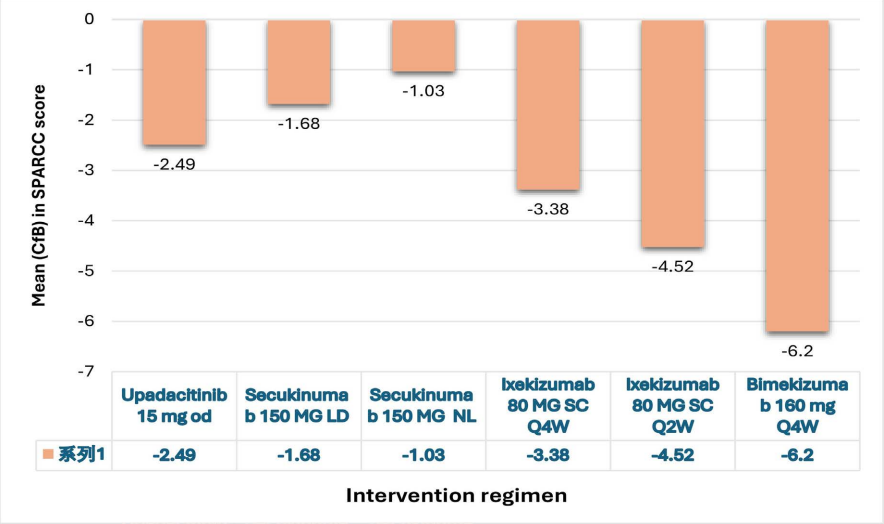

Figure 8. SPARCC MRI sacroiliac joint score upadacitinib at week 14, IL-17i at week16.

3.1.9. MRI Spine

Spinal MRI images were assessed for signs of inflammation using the SPARCC MRI spine changes from baseline or Berlin modification of the AS spine MRI. Typical lesions of the spine, which indicate active disease, are spondylitis, spondylodiscitis, and arthritis of the facet, costo-vertebral and costo-transverse joints. MRI Berlin spine score ranges from 0 to 69; lower scores indicate less spinal inflammation, and negative changes represent improvements which were checked as change from baseline (CfB). In bimekizumab groups, 57.5% (146/254) of patients had Berlin spine assessments. The mean change from baseline in spine inflammation was almost double in upadacitinib treated patients at week 14 compared to bimekizumab treated patients at week 16, (−0.79) versus (−0.4) respectively.

3.2. Efficacy Data at Week 52

3.2.1. ASAS40 Response Rates

The ASAS40 response was sustained and comparable up to week 52 between treatment arms (intervention initial randomization and open label) among all the trials (p value < 0.05, 95 % CI). The percentage of patients achieving ASAS40 continued to be slightly higher with upadacitinib (63%) and comparable to bimekizumab (62%) through week 52. Patients who received ixekizumab in either dose achieved a mean of 30.5% ASAS40 response rate. The lowest ASAS40 achievement was achieved in those who received secukinumab with or without loading dose (19%), see Figure 9.

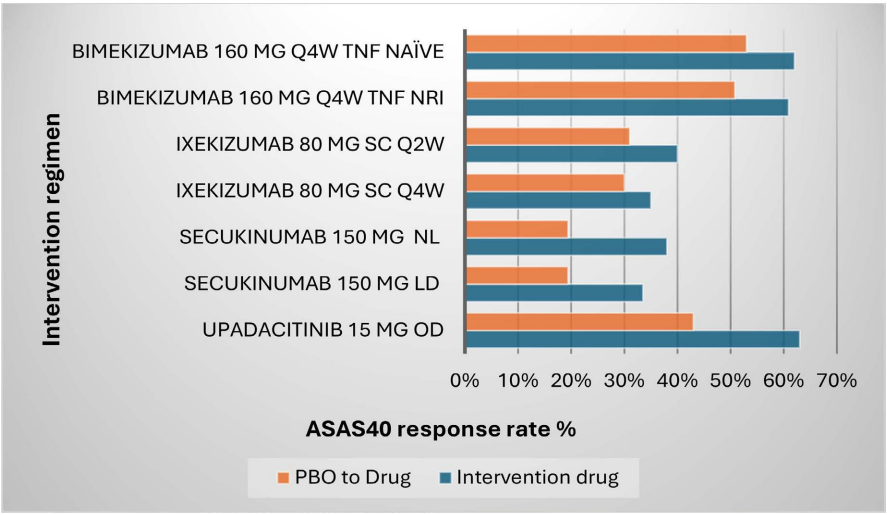

Figure 9. ASAS40 response rates at week 52, intervention versus placebo.

3.2.2. Secondary Outcome Measures

Statistically significant improvements in most secondary endpoints were also demonstrated in interventions groups versus corresponding placebo at week 52 across both JAKi and IL-17i trials (p value < 0.05, 95 % CI). The proportions of patients achieving ASDAS LDA (ASDAS < 2.1) and ASDAS ID (ASDAS < 1.3) by Week 52 were comparable among JAKi and IL-17i. In other words, upadacitinib versus bimekizumab treated patients achieved ASDAS LDA (55.8%), versus 61.6%, in bimekizumab initial randomization (BKZ) and 54.5% in those who switched from placebo to bimekizumab (PBO/BKZ). Similarly, ASDAS ID was (32.7%) in upadacitinib arm compared to around a quarter of patients in bimekizumab arms, (BKZ: 25.2% and PBO/BKZ: 28.0%). Among the rest of the encountered outcome measures (ASAS20, ASAS PR, BASDAI50), both upadacitinib and bimekizumab treated individuals achieved a comparable score, see Figure 10 below. Mean change from baseline (CfB) at week 52 in encountered measures addressing pain, physical function and quality of life such as total back pain (TBP), nocturnal back pain (NBP), BASFI and ASQoL were also comparable between upadacitinib and bimekizumab treated patients. For instance, upadacitinib demonstrated improvement through week 52 in total back pain (−4.22, p < 0.05)

compared to (−4.2) in BKZ an-4) in PBO/BKZ. Likewise, upadacitinib demonstrated sustained improvements in hs-CRP (−6.91, $p < 0.001$) compared to (−5.9) and (−5.3) in BKZ and PBO/BKZ respectively, see Figure 11.

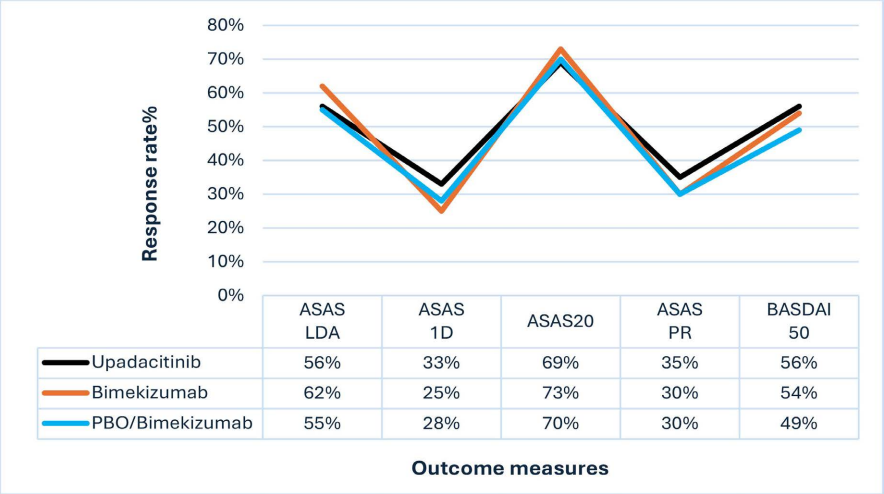

Figure 10. Upadacitinib vs bimekizumab in some secondary endpoints at week 52.

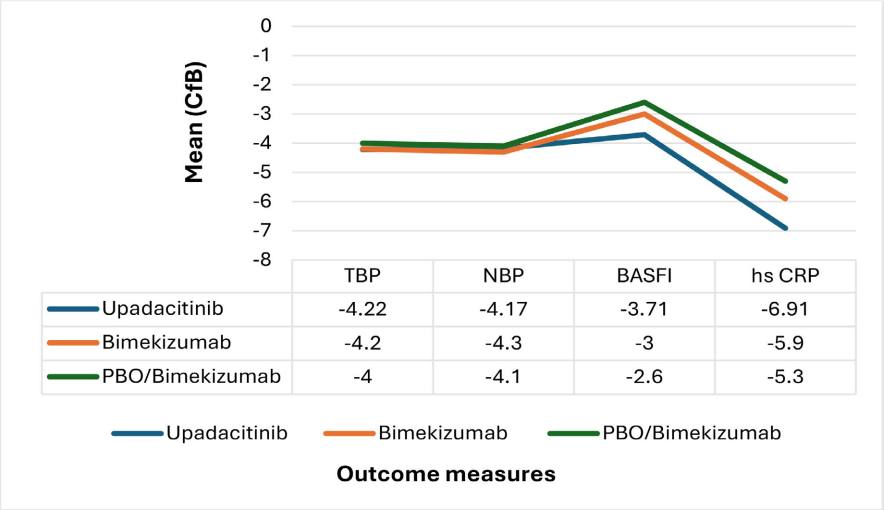

Figure 11. Upadacitinib vs bimekizumab in pain, physical function and hs-CRP at week 52.

3.3. Safety Data

Overall, the safety of upadacitinib, secukinumab, ixekizumab and bimekizumab remained consistent with previously reported safety data in trials of these agents in other auto immune diseases.

Treatment emergent adverse events (TEAEs) were approximately similar across our four studied drugs and its corresponding placebos indicating comparable safety profiles. The presence of any adverse event was lower in JAKi-upadacitinib treated patients (48%) compared to IL-17i (72% in ixekizumab, 62% in bimekizumab and 61% in secukinumab treated patients). It is worth noting that safety

data were reported up to week 14 in upadacitinib, to week 20 in secukinumab, and to week 52 in ixekizumab and to bimekizumab groups.

3.3.1. The Most Frequent TEAEs

The most frequent TEAEs vary among each drug; for instance, in bimekizumab group (n = 244), the commonly encountered adverse events were: nasopharyngitis (30 patients) 12.3%; upper respiratory tract infections (23 patients), 9.4%; oral candidiasis (20 patients), 7.4%; and Corona virus infection (17 patients), 7%. Note, SELECT AXIS2 was conducted during the COVID-19 pandemic; even though, upadacitinib treatment was not associated with increased COVID-19 infection compared with placebo.

Similarly, in secukinumab pooled group, the commonest adverse event up to week 20 (n = 369): nasopharyngitis (46 patients), 12.5%; diarrhea (23 patients), 6.2%; headache (22 patients), 6%; and upper respiratory tract infections (22 patients), 6%. Of notes, patients who were treated with ixekizumab (n = 198) shared the same common adverse events mentioned above; in addition, they experienced more injection site reaction (28 patients), 14.1%; and hypertension (10 patients), 5%. The majority muco-cutaneous infections were mild to moderate, treated with standard anti-fungal drugs and did not lead to treatment discontinuation.

3.3.2. Serious Adverse Events (SAEs)

SAEs were encountered in 4 patients treated with upadacitinib versus 2 in those who received placebo, and all were due to other risk factors. In comparison, 9 out of 244 (3.7%) bimekizumab treated patients developed SAEs. While it was around 1.5% (3 out of 198) in patients who received ixekizumab and approximately 0.8% (3 out of 369) in secukinumab treated patients, see Figure 12.

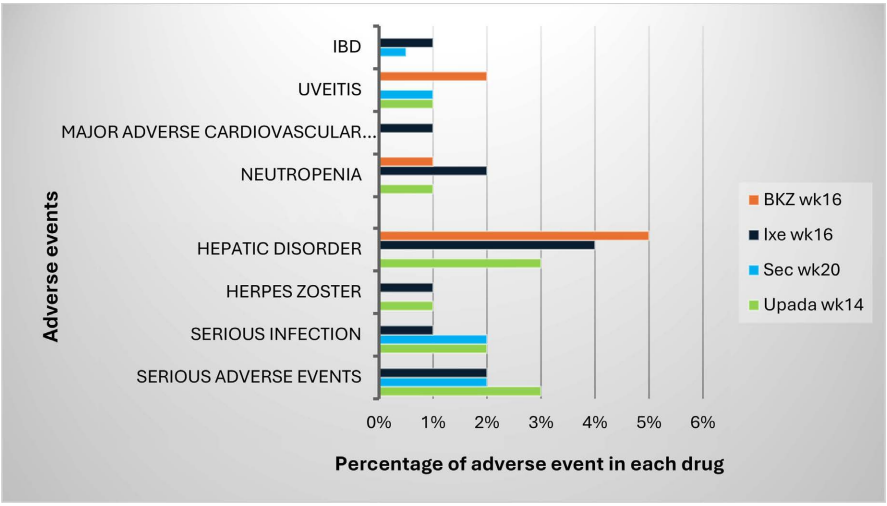

Figure 12. Other adverse events.

3.3.3. Other Adverse Events

Inflammatory bowel disease (IBD) related events more of flare or recurrence were reported in IL-17i while mild to moderate herpes zoster venous thromboembolic

events (VTE) were seen with JAKi treatment. The reported hematological and hepatic abnormalities such as anemia, neutropenia, and elevated liver enzymes were non serious and did not result in study drug discontinuation. A higher number of patients in secukinumab groups had uveitis, 11 patients were reported; however, all were mild to moderate in severity, and none had led to treatment discontinuation. Only one case of iridocyclitis in bimekizumab treated patients led to treatment discontinuation.

Overall, no deaths, serious opportunistic infections, active tuberculosis, or adjudicated major adverse cardiovascular events (MACE). Some malignancy events were reported in secukinumab and bimekizumab treated patients. One case of renal cell carcinoma in a patient treated with bimekizumab and three cases of malignancy in secukinumab treated patients (malignant melanoma, squamous cell carcinoma of the tongue, and basal cell carcinoma). All these events were evaluated and found to be not related to any study medication as considered by the investigators.

4. Discussion

Overview, strength and limitations

In this systematized review, we focused on the treatment of active nr-ax SPA, comparing the efficacy and safety of the only approved JAKi (upadacitinib) with the only approved IL-17i so far, (secukinumab, ixekizumab and bimekizumab). To the best of our knowledge, there is no similar comparative study of JAKi versus IL-17i in patients with active nr-ax SpA.

The strength and importance of this review is that it included the four randomized control trials which constituted the basis on which these agents were approved for the treatment of patients with active nr-ax SPA. SELECT-AXIS 2 is the first study to document the efficacy and safety of a JAK inhibitor in nr-ax SPA. Similarly, PREVENT is the first and the largest randomized controlled trial of a biologic therapy in non-radiographic axial SpA to date. Secukinumab and ixekizumab were approved for nr-ax SpA by the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) based on the positive results of PREVENT and COAST-X trials, [4]. In 2023, bimekizumab was also approved by EMA based on results obtained from BEMOBILE1. Moreover, these RCTs investigated patients with different backgrounds treatment medications including biologics. For instance, SELECT-AXIS 2 trial intentionally enrolled about a third of patients who had an inadequate response to bDMARDs, namely, TNFi and IL-17i, representing a more population (treatment-refractory patient). Such subgroups of patients with inadequate response to bDMARDs comprised patients who are usually less likely to be responders because of: older age, longer disease duration, and less objective signs of active inflammation (high-sensitivity C-reactive protein or MRI). Additionally, the retention rates were high among these RCTs, with 95.0% of randomized patients completing week 24% and 86.7% completing week 52 in SELECT AXIS2 trial and 244 out 254, (96.1%) patients

randomized in BEMOBILE 1 completed week 16, and 220 (86.6%) completed to week 52. In COAST-X study, (96%) 290 out of 303 randomized patients completed the first 16 weeks and (87%) 265 patients completed the whole 52 weeks, including those who switched to open-label ixekizumab Q2W. Similarly, in PREVENT trial 95% of patients completed week 24 and 86.7% completed week 52.

The main limitation of this review is that the analyses was restricted to 4 studies that met the inclusion criteria. In addition, some limitations are related to the included RCTs such as: absence of an active comparator, a small sample size of patients who had an inadequate response to IL-17 inhibitors, and the absence of longer-term data represent the main limitations in upadacitinib trial, (SELECT AXIS2). In bimekizumab trial (BEMOBILE1) lack of placebo control after week 16 was one of the important limitations as patients were aware that they had been receiving active treatment from weeks 16 through 52.

Efficacy data

Achievement of clinical efficacy outcomes was overall in line with what has been reported in other ax SpA trials in which patients were treated with TNF, JAKi, and/or IL-17i. The primary outcome measure (ASAS40) response rate was met in all RCTs, and all agents demonstrated statistically significant improvement compared to placebo. However, when compared to each other it was significantly higher in patients treated with bimekizumab 160 mg sc Q4wks in TNF NRI at week 16 (48%) and TNF naïve (47%) followed by upadacitinib 15 mg PO OD at week 14 (45%). This could be explained by the dual blocking effect of bimekizumab of both IL-17A and IL-17F. This argument could further be supported by the fact that the inhibition of JAK STAT pathway blocks several inflammatory cytokines at the same time as mentioned above. Nevertheless, the percentage of patients achieving ASAS40 were closely similar at week 52 in both upadacitinib (63%) and in bimekizumab (62%).

Most of the predefined secondary endpoints addressing disease activity, physical function, and quality of life were met and comparable. Of note, enthesitis and BASMI were only evaluated in upadacitinib and bimekizumab treated patients. Around 73% (186 out of 254) of bimekizumab treated patients at baseline had enthesitis with (MASES > 0) and only 54.3% of them achieved complete resolution MASES = 0). Similarly, change from baseline in MASES in upadacitinib treatment arm was not statistically significant. It is worth noting that BASMI was not statistically significant among both upadacitinib and bimekizumab treatment arms compared to placebo; this could be attributed to the fact that restriction in range of motion occurs late during axial SPA, which is not the case in this form of early axial SPA, the nr-ax SPA.

Interestingly, post hoc analysis of data from ABILITY-1, a phase 3 trial of adalimumab vs placebo in nr-ax SpA, have shown that ASAS40 and ASDAS responses were associated with statistically significant and clinically relevant improvements in patients' reported outcomes of physical function, HRQL and work productivity, [11]. These findings support the use of these measures for monitoring disease

activity in patients with nr-ax SpA in clinical practice and in clinical trials.

Safety data

As mentioned above, the safety of JAKi and IL-17i were consistent with previously reported safety data up to two years in other trials which had evaluated these agents' efficacy and safety in other auto immune diseases such as: ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. It is worth emphasizing that in this review the safety data were reported in a short-term follow-up (14 weeks) in upadacitinib and relatively short-term (20 weeks) in secukinumab treated patients compared to 52 weeks in both ixekizumab and bimekizumab treatment arms. Thus, safety profile should be carefully looked at in these groups.

The treatment emergent adverse events TEAEs or any adverse events were comparable among all these agents, however, it was hard to attribute the encountered events to the intervention drugs. In general, infections were mild to moderate and significantly higher in IL-17i treated patients. It is worth emphasizing that screening for latent TB and viral infections along with immunization according to the national and international guidelines are mandatory as well as avoidance or cautious use in patients at higher risk of infections. Hopefully, no increased risk of thrombotic events, MACE, malignancy, life threatening events or death were documented.

Current practice guidelines

According to the joint Assessment of Spondyloarthritis International Society (ASAS) and European League Against Rheumatism (EULAR), ASAS-EULAR recommendations for the management of axial spondyloarthritis, 2022 update: "the primary goal of treating patients with ax SpA, is to maximize health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, and preservation/normalization of function and social participation", [12].

The optimal management of patients with ax SpA requires a combination of non-pharmacological and pharmacological treatment modalities. The non-pharmacological measures include the education of patients about the disease to get their input to make a shared management plan, regular exercises, smoking cessation and physical therapy.

Pharmacological management:

Non-steroidal anti-inflammatory drugs: According to ASAS-EULAR, NSAIDs are recommended as first-line drugs for patients with ax SpA. It relieves pain and stiffness in up to 60% - 70% of the patients and achieve partial remission in up to 15% of patients with active ax SPA. The effect of NSAIDs on high sensitivity C-reactive protein (CRP) and bone marrow oedema (BMO) or on the radiographic progression of patients with ax SpA is still unclear. The question of whether it is advisable to continue treatment with NSAIDs even in, or after reaching a status of low disease activity is a matter of discussion. However, a full dose for at least two weeks is recommended as the first line of treatment for patients suffering from

pain or stiffness. If there is no response or inadequate response, a trial of another class of NSAIDs before moving to the second line of treatment.

Corticosteroids: long-term systemic steroids use is not recommended in patients with axial disease. In patients who are intolerant or have contraindications to NSAIDs, steroids could be helpful in patients with peripheral joint manifestations, and local steroids injections of articular and/or peri articular manifestations may be considered.

Conventional synthetic DMARDs:

The csDMARDs are not recommended for purely axial disease due to their lack of efficacy. Unlike methotrexate, sulfasalazine demonstrated efficacy in subgroups of patients with peripheral arthritis.

Biological and targeted synthetic DMARDs:

In patients who failed or responded inadequately to NSAIDs, TNFi were the only alternative option for quite a long time. Currently, other biologics and molecules targeting agents were introduced and approved for the treatment of ax SpA (radiographic and non-radiographic. These include interleukin 17 inhibitors and janus kinases inhibitors, the subject of this review. TNFi, IL-17, and JAKi were all proven to have a comparable efficacy in achieving treatment goals with some variation in safety profiles, [13].

TNF inhibitors (TNFi) improve axial and peripheral SPA, enthesitis, dactylitis and many extra articular manifestations in addition to inflammatory markers and MRI-evident inflammation at SIJs/spine. Although TNFi are effective in controlling inflammation and prevention of joint destruction, it does not prevent new bone formation indicating presence of other pathogenic pathways. Furthermore, it may not maintain sustained remission; studies have shown that in up to 50% of patients, clinically significant response was not achieved, [14].

IL-17 constitutes a family of cytokines including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL17F. In patients with nr-ax SPA, serum levels of IL-17A were demonstrated to be higher in patients with positive MRI findings than in patients with negative MRI, [15]. Among the available IL-17i, secukinumab (anti IL-17A), ixekizumab (anti-IL-17A), and in 2023 bimekizumab (anti-IL-17A & IL-17F) are approved for the treatment of nr-ax SpA. Other IL-17 inhibitors such as brodalumab (anti-IL-17RA) are still under evaluation.

The JAK/STAT pathway is involved in the signaling of various molecules and implicated in the pathogenesis of autoimmune, allergy, and inflammatory conditions such as SPA, [16]. There are 4 JAK proteins (JAK1, JAK2, JAK3, and TYK2) and 7 signal transducer and activator of transcription (STAT). Different JAK inhibitors target these subtypes with variable degree of selectivity and control of the underlying inflammatory processes. Both tofacitinib and upadacitinib are approved for AS, (r-ax SpA).

The current practice data suggests that rheumatologists prefer to start TNFi because of relatively longer experience, and more safety profile data. The National Institute for Health and Clinical Excellence (NICE) as well as ACR recommends

and support the use of IL-17i in patients with nr-ax SpA who cannot tolerate or have failed a TNFi. The treatment of patients with ax SpA should be tailored according to the disease pattern axial, entheseal, peripheral, extra-musculoskeletal manifestations (EMMs), and patient characteristics. For instance, in patients with a history of recurrent uveitis or active IBD, priority should be given to TNFi; while in those with significant psoriasis, an IL-17i may be preferred. Switching between bDMARD with a different mechanism of action should be considered in case of treatment failure. If sustained remission is achieved, tapering of a bDMARD can be considered, usually through drug Spacing.

Residual pain is a frequent problem encountered in clinical practice, particularly axial SpA. The ASAS/EULAR recommend analgesics, such as paracetamol and opioid/opioid-like drugs to treat residual pain bearing in mind risk benefit profiles. Finally, the optimum management of patients rest on multi-disciplinary team depending on the disease presentation and system involvement led by a rheumatologist and based on early diagnosis and early institution of treatment.

5. Conclusion

Overall, all these medications were well found to have a comparable efficacy data, well tolerated, with reasonable and comparable safety profiles. Until today and to the best of our knowledge, there is no a head-to-head trial comparing JAKi versus IL-17i in patients with active nr-ax SpA; therefore, such study is required to demonstrate superiority (if any) of either agent over the others. JAKi as well as IL-17i are an essential treatment for patients with active nr-ax SpA particularly those with contraindications, intolerance, or inadequate responder to TNFi. The evidence encountered from different RCTs in this review was in line with current existing data in terms of efficacy and safety of these agents either in r-ax SpA or other systemic auto immune diseases.

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Conflicts of Interest

The authors have no competing interest to declare.

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Appendix 1

Important definitions of different outcome measures:

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index is a tool used to evaluate ankylosing spondylitis activity, a score of ≥4 and total back pain score of ≥ 4 on a (0 - 10 scale) indicate active disease.

BASDAI50: is defined as a 50 % improvement in baseline Bath Ankylosing Spondylitis Disease activity index, domains include:

- Fatigue/tiredness
- Level of AS neck, back or hip pain
- Level of pain/swelling in joints other than neck, back, or hips
- Level of discomfort from any areas tender to touch or pressure
- Level of comfort when waking up
- Duration of morning stiffness

ASAS40 response rate is defined as an improvement of 40% or more plus an absolute improvement from baseline of 2 or more units (range 0 - 10) in at least three out of four assessments domains with no worsening in the remaining one, (Cheung, 2017). The four ASAS assessment domains are:

- Patient global assessment
- Spinal pain
- Physical function from BASFI
- Inflammation/morning stiffness

ASAS20 response rate is defined as at least 20% improvement from baseline and an absolute improvement from baseline of at least 1 unit (on scale 0 - 10) in at least three out of four ASAS assessment domains, and no worsening > 1 unit in the remaining one of the four domains.

ASAS PR: ASAS partial remission is indicated by a score of <2 in each of the four ASAS assessments domains.

ASDAS: the Ankylosing Spondylitis Disease Activity Score is a composite index that assesses disease activity incorporating three items from the BASDAI: back pain (10 cm VAS), duration of morning stiffness (10 cm VAS) and pain/swelling of peripheral joints (10 cm VAS), as well as patient global assessment of disease activity (10 cm VAS) and a laboratory measure of inflammatory markers, CRP level (in mg/l) or ESR (in mm/h). Disease activity state has been defined as:

- Inactive (ASDAS < 1.3)
- Moderate (ASDAS ≥ 1.3 to <2.1)
- High (ASDAS ≥ 2.1 to <3.5)
- Very high (ASDAS > 3.5)

BASFI is a tool used to evaluate functional capacity based on 10 questions and it is available online. The first 8 questions evaluate activities related to functional anatomical limitations related to the disease and the final 2 questions evaluate the patients' ability to cope with day-to-day life.

SPARCC MRI score: the entire spine is evaluated for inflammation, but only the 6 most severely affected disco-vertebral units are scored. Each SI joint is

divided into 4 quadrants: upper and lower iliac, upper and lower sacral. The presence of an increased signal on STIR is assigned a point, depending on intensity and depth of signal. The score is repeated in 6 consecutive slices and ranges from 0 to 72.