New pharmacologic treatment options for ankylosing spondylitis- JAK inhibitors

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Abstract

Aims: This review aims to present the current knowledge on the efficacy and safety of a new therapeutic option approved for the treatment of ankylosing spondylitis - JAK inhibitors: upadacitinib and tofacitinib. These therapies may benefit patients with an inadequate response to or intolerance of NSAIDs or bDMARDs.

Material and methods: A systematic search of PubMed was conducted, focusing on the past ten years and selected studies from key years. The search strategy included relevant keywords related to Janus kinase (JAK) inhibitors, ankylosing spondylitis (AS), upadacitinib, and

tofacitinib. The most pertinent articles aligned with the study objective were reviewed and included.

Results: Seventeen publications were included in the review, comprising ten clinical studies and seven secondary analyses or review articles. Clinical studies demonstrated improvement in ASAS40, ASDAS, BASFI, and BASDAI50 scores, reduced spinal and sacroiliac inflammation, and improved quality of life in patients with AS treated with tofacitinib or upadacitinib. The most frequently reported adverse events were mild to moderate in severity. No new adverse events were observed beyond those already known and consistent with the established safety profile of JAK inhibitors. Post hoc analyses and review papers confirmed the findings of clinical studies and provided additional insights into selected patient subgroups.

Conclusions: Tofacitinib and upadacitinib are effective and reasonably safe for AS, including patients who do not respond to or tolerate NSAIDs or bDMARDs. They offer a favorable benefit–risk balance and are viable options after first-line failure, though more long-term data are needed.

Keywords: **AS**, **JAK inhibitors**, **tofacitinib**, **upadacitinib**

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease classified as a form of axial spondyloarthritis (axSpA). It mainly affects the spine, sacroiliac joints, and peripheral joints, causing severe chronic back pain and stiffness [1,2]. Symptoms are typically worse at night and after periods of rest, improving with exercise. The disease has an insidious onset and can lead to hyperkyphosis and disabling spinal fusion [3]. The imaging characteristics of AS include erosions with bony growths, syndesmophytes, ankylosis of the interapophyseal joints, calcification of spinal ligaments and progressive ankylosis [1]. In addition, it can present with extra-axial manifestations, such as enthesitis and peripheral articular symptoms, as well as extra-articular manifestations - uveitis, psoriasis, inflammatory bowel disease, diabetes mellitus, osteoporosis, cardiac involvement and increased cardiovascular risk [4,5,6]. However, peripheral arthritis is less common, tends to be asymmetric, and usually involves a single large joint, such as the hip, knee or shoulder [3]. The disease typically manifests around the age of 30 and is more prevalent in men [7,6]. Nevertheless, female patients tend to exhibit more severe active phases and to develop fatigue earlier than males [6].

The pathogenesis of AS is not yet fully understood. However, the foundation of the disease lies in an autoimmune inflammatory response, where the IL-23/IL-17 pathway plays a central role. IL-23, secreted by antigen-presenting cells promotes differentiation of T-cells into pro-inflammatory Th17 cells, which in turn produce IL-17A - a cytokine that enhances inflammation particularly in mucosal tissues and joints [8]. The pathological changes in AS start in the synovium of the sacroiliac joints, characterized by infiltration of lymphocytes and plasma cells. Over time, these joint spaces become obliterated and ossified. As the disease progresses, similar inflammatory and ossifying changes affect the spine, resulting in syndesmophytes - bony bridges that connect adjacent vertebrae. From a genetic perspective, the HLA-B27 antigen plays a significant role. This molecule has a tendency to misfold, form homodimers, and present improperly processed peptides, which can trigger an autoimmune response. These abnormalities contribute to chronic inflammation and structural damage within the axial skeleton [4].

The advancement of AS depends on complex reciprocations between genetic, immunological and environmental factors. The most significant genetic risk factor is the presence of the HLA-B27 allele. Although the exact molecular mechanism remains unclear, HLA-B27 polymorphisms affect antigen presentation and peptide binding, possibly promoting autoimmunity. Furthermore, studies indicate the influence of many factors underlying AS, such as genetic predisposition, lifestyle, smoking, exposure to heavy metals and environmental pollutants [8].

There are several classification criteria for AS, including the modified New York (mNY) criteria and ASAS criteria for axSpA [9]. Axial spondyloarthritis is further classified into AS and non-radiographic axial spondyloarthritis (nr-axSpA). These two forms may be considered progressive stages of the same disease, distinguished by sacroiliitis on radiographic imaging, as defined by the mNY criteria [4]. The ASAS criteria apply to patients with chronic back pain lasting at least 3 months, starting before the age of 45. The criteria also require the presence of sacroiliitis on radiography or MRI, with at least one additional clinical feature of SpA or at least two clinical features in the presence of HLA-B27 [9]. Meanwhile, the mNY criteria include radiographic criterion of sacroiliitis and clinical criteria, such as low back pain and stiffness, limited lumbar spinal motion and reduced chest expansion [5].

Treatment of AS primarily involves nonsteroidal anti-inflammatory drugs (NSAIDs), while patients with high disease activity often require biological therapies. Key treatment options include TNF-α inhibitors (TNFi) – such as adalimumab and etanercept – block tumor necrosis factor alpha, a key inflammatory mediator in AS. IL-17 inhibitors– such as secukinumab and ixekizumab – act by blocking IL-17A, thus suppressing Th17 cell activity and inflammation in the axial skeleton [7].

Treatment efficacy is evaluated using standardized scales: BASDAI – measures disease activity through 6 patient-reported questions. It covers fatigue, spinal pain, joint pain/swelling, enthesitis, duration of morning stiffness and severity of morning stiffness. Each question is rated on a 0-10 scale, where 0 means 'no problem with it' and 10 means 'worst possible' and a score higher than 4 indicates high disease activity. BASFI – assesses functional limitations and daily living capability. It covers 8 questions on physical activities (like bending, reaching or walking) and 2 on overall impact on daily life. It's scored on the scale 0-10 (where 0 means easy and 10 means impossible); BASMI – evaluates spinal mobility; it includes 5 clinical measurements: finger-to-floor distance, Schober's test, occiput-to-wall distance, chest expansion and cervical rotation; it's rated on a scale 0-10 (where 0 is unrestricted movement and 10 is a severe limitation). Finally ASAS20, ASAS40, ASAS5/6 – composite indices indicating improvement (e.g., ASAS40 represents a 40% improvement in at least 3 out of 4 core criteria). Also ASDAS is a useful tool, it combines patient-reported measures with objective inflammatory markers (CRP or ESR). Score interpretation of ASDAS is: <1,3 inactive disease (remission); 1.3-2.1 - low disease activity; 2.1-3.5 - high disease activity; >3.5 - very high disease activity [9].

ASAS 20 represents improvement of $\geqslant$20% and $\geqslant$1 unit in 3 of 4 domains like patient global assessment, spinal pain, BASFI or inflammation per BASDAI; ASAS40 represents improvement of $\geqslant$40% and $\geqslant$2 units in 3 of 4 domains; therefore ASAS5/6 represents improvement of $\geqslant$20% in $\geqslant$5 of 6 domains (4 as above + spinal mobility and CRP level additionally).

Despite significant advances in targeted therapies, the need for continued research remains, particularly for patients with refractory disease.

Results

JAK Inhibitors

JAK inhibitors are immunomodulatory drugs that inhibit the Janus kinases: JAK1, JAK2, JAK3, and TYK2. Their aim is to block the JAK-STAT pathway, through which cytokines transmit signals to the cell nucleus, contributing to the expression of pro-inflammatory genes. This mechanism is implicated in diseases such as rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, atopic dermatitis, myelofibrosis, polycythemia vera, and ankylosing spondylitis.

JAK inhibitors suppress activation of the JAK-STAT signaling pathway, which plays a key role in ankylosing spondylitis. Activation of JAK kinases leads to activation of STAT proteins,

which in AS drive a chronic inflammatory response, resulting in symptoms such as back pain and spinal stiffness.

1. Upadacitinib

The efficacy and safety of upadacitinib (UPA), a selective JAK1 inhibitor, in patients with ankylosing spondylitis (AS) were evaluated in the multicenter, randomized, double-blind, placebo-controlled phase 2/3 SELECT-AXIS 1 trial. The study enrolled 187 adult AS patients from 62 sites in 20 countries who met the modified New York criteria, had not previously received JAK inhibitors or any biologic therapy that could affect AS, and had an inadequate response to at least two nonsteroidal anti-inflammatory drugs (NSAIDs) or had contraindications/intolerance to their use. Patients were randomized 1:1 to receive oral UPA 15 mg once daily or placebo.

After 14 weeks, efficacy was assessed using the composite response criteria of the Assessment of SpondyloArthritis International Society (ASAS). The ASAS40 response rate was 52% with upadacitinib versus 26% with placebo ($p = 0.0003$). For ASDAS, the mean change from baseline was −1.45 (95% CI, −1.62 to −1.28) with UPA versus −0.54 (95% CI, −0.71 to −0.37) with placebo ($p < 0.0001$). Improvement in BASFI was also greater with UPA: mean change from baseline −2.29 (95% CI, −2.73 to −1.85) versus −1.30 (95% CI, −1.74 to −0.86) with placebo ($p = 0.0013$). BASDAI50 was achieved by 45% of patients on UPA versus 23% on placebo ($p = 0.0016$). ASAS partial remission was achieved by 19% on UPA and 1% on placebo ($p < 0.0001$).

For SPARCC MRI of the spine, the change from baseline was −6.93 (95% CI, −8.58 to −5.28) with UPA versus −0.22 (95% CI, −2.01 to 1.57) with placebo. For SPARCC MRI of the sacroiliac joints, the mean change from baseline was −3.91 (95% CI, −5.05 to −2.77) with UPA versus −0.22 (95% CI, −1.47 to −1.04) with placebo. Low disease activity by ASDAS was observed in 49% of UPA-treated patients versus 11% on placebo, while inactive disease was seen in 16% versus 0%, respectively. Clinically important improvement in ASDAS was achieved by 53% with UPA and 35% with placebo ($p < 0.0001$).

Other multiplicity-controlled secondary endpoints did not reach statistical significance in the multiplicity testing procedure but showed consistent improvements versus placebo in ASQoL,

BASMI, MASES, and the ASAS Health Index (nominal p <0.05), with the exception of WPAI. Improvement was evident at the first visit and remained stable through week 14 [10]. In the 2-year open-label extension, 187 patients were enrolled; of these, 144 completed week 104. Efficacy was assessed using as-observed (AO) and non-responder imputation (NRI). An increase in the ASAS40 response among patients receiving continuous UPA was observed during weeks 32–40, after which responses plateaued and were maintained through week 104 at 85.9% (AO) and 65.6% (NRI). In the PBO→UPA group, ASAS40 was 88.7% (AO) and 63.8% (NRI) at the end of the study.

The mean change from baseline in BASFI by mixed-effects model for repeated measures (MMRM) was −3.50 (95% CI, −3.85 to −3.14) in the continuous-UPA group and −3.26 (95% CI, −3.62 to −2.91) in the PBO→UPA group.

Among patients employed at baseline, the mean (95% CI) Work Productivity and Activity Impairment (WPAI) overall work impairment score continued to improve over the course of the study in the continuous-UPA group (from −20.5 [−27.1 to −14.0] at week 14 to −34.5 [−44.2 to −24.7] at week 104; AO) and in the group switched from placebo to upadacitinib (from −12.3 [−19.8 to −4.8] at week 14 to −28.3 [−36.7 to −19.8] at week 104). Similar results were obtained in the MMRM analysis.

SPARCC MRI inflammation scores of the spine and sacroiliac joints remained stable in the continuous-UPA group, and patients in the PBO→UPA group achieved a similar magnitude of improvement by week 104. Based on radiographic spine readings, the mean (95% CI) change in mSASSS from baseline to week 104 was 0.7 (0.3 to 1.1) overall (continuous UPA, 0.6 [0.1 to 1.1]; PBO→UPA, 0.8 [0.2 to 1.4]). No radiographic progression at week 104—defined as a change from baseline in mSASSS <2—was observed in 89.7% of patients, and no change from baseline (≤0) in 76.5%.

Factors associated with the greatest mSASSS progression over two years were male sex, HLA-B27 positivity, higher baseline mSASSS and CRP, and a positive smoking history (current or past) [11].

In a phase III study conducted by van der Heijde et al., 420 patients with ankylosing spondylitis (AS) and an inadequate response (IR) to biologic disease-modifying antirheumatic drugs (bDMARDs) were randomized to receive double-blind oral upadacitinib 15 mg once daily or placebo for 14 weeks. The study was completed by 98% of patients in the UPA group and 97%

in the placebo group. At week 14, the ASAS40 response rate was 45% with UPA versus 18% with placebo ($p < 0.0001$). Improvement in the UPA group was observed from week 4 (nominal $p \leq 0.05$). ASAS40 was achieved by 46% of patients in the UPA subgroup previously treated with one bDMARD versus 20% with placebo, and by 36% of those previously treated with two bDMARDs versus 4% with placebo. Greater ASAS40 improvements with UPA were also seen regardless of prior mechanism: following prior TNF-inhibitor exposure, 47% versus 22%; after prior IL-17 inhibitor exposure, 37% versus 4%.

Across baseline hsCRP strata, greater ASAS40 improvements were observed in all UPA subgroups; among patients with baseline hsCRP >5 mg/L, the rate was 44% with UPA versus 20% with placebo. On SPARCC MRI, improvement in the spine was −3.95 with UPA versus −0.04 with placebo, and in the sacroiliac joints, −2.26 versus −1.05, respectively.

Statistically significant improvements in disease activity, function, and pain were seen with UPA versus placebo at week 14, measured by change from baseline in ASDAS (CRP; −1.52 vs −0.49), total and nocturnal back pain, and BASFI (−2.26 vs −1.09), as well as achievement of ASDAS inactive disease (13% vs 2%), ASDAS low disease activity (44% vs 10%), BASDAI50 (43% vs 17%), ASAS20 (65% vs 38%), and ASAS partial remission (18% vs 4%; all $p < 0.0001$). Improvements were also observed in quality of life (ASQoL and ASAS Health Index), spinal mobility (BASMI), and enthesitis (MASES) in the UPA group ($p < 0.0001$) [12].

In the 2-year open-label extension (OLE), 409 patients were enrolled, of whom 331 completed week 104. Improvements in efficacy endpoints were maintained through the end of the study. The ASAS40 rate by as-observed/non-responder imputation (AO-NRI) at week 104 increased to 64.9% in the continuous-UPA group and to 61.7% in the placebo→upadacitinib (PBO→UPA) group. The ASAS20 rate rose in the continuous-UPA group from 65.4% at week 14 to 72.5% at week 104, and in the PBO→UPA group from 38.3% to 75.6%.

By mixed-effects model for repeated measures (MMRM), the mean change from baseline at study end in hsCRP was −10.1 in both the continuous-UPA group (95% CI, −11.6 to −8.7) and the PBO→UPA group (95% CI, −11.5 to −8.6); for BASFI it was −3.8 (95% CI, −4.1 to −3.5) with continuous UPA and −3.7 (95% CI, −4.1 to −3.4) with PBO→UPA.

Other week-104 efficacy assessments—mean changes from baseline—were similar between groups across measures (ASDAS: −2.1 and −2.0; total back pain: −4.9 and −4.6; as-observed mixed-effects model for repeated measures, AO-MMRM). In more than 93.0% of patients, no

radiographic progression was observed by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), defined as a mean change from baseline <2 [13].

2. Tofacitinib

Tofacitinib, which preferentially inhibits signalling via JAK3 and/or JAK1 with functional selectivity over signalling via pairs of JAK2, had its dose range for patients with ankylosing spondylitis (AS) established in a 16-week, randomized, placebo-controlled phase II trial. The study enrolled 208 adults with AS who met the modified New York criteria, had a BASDAI ≥4 and a back-pain score ≥4, and had received inadequate treatment with at least two oral NSAIDs (or were NSAID-intolerant). Patients could continue concomitant methotrexate, sulfasalazine, and stable oral corticosteroids (<10 mg/day of prednisone or equivalent).

Participants were then randomized (1:1:1:1) to receive placebo or tofacitinib 2, 5, or 10 mg twice daily for 12 weeks, followed by a 4-week observation period. The key efficacy endpoint was the ASAS20 response at week 12 using non-responder imputation (NRI), in 196 patients who completed the study. Analyses included 51 patients on placebo and 52 in each tofacitinib dose group. According to the Emax model, the predicted response rate for the 10 mg dose was 67.4%, the highest among all doses and placebo. Observed ASAS20 rates were 40.1% for placebo, 56% for 2 mg, and 63% for 5 mg. By normal approximation, comparing active treatment with placebo, response rates were significantly greater with tofacitinib 5 mg twice daily versus placebo ($p < 0.001$), but not with 2 or 10 mg twice daily.

Other efficacy endpoints included ASAS40 (46.2% with tofacitinib 5 mg vs 19.6% with placebo), BASDAI50 (42.3% with 5 mg vs 23.5% with placebo), ASDAS clinically important improvement (63.5% with 5 mg vs 27.5% with placebo), and the Berlin MRI score (−2.20 for 5 mg and −2.13 for 10 mg vs −0.41 for placebo; $p < 0.001$ and $p = 0.001$). Significant improvements in SPARCC scores for the sacroiliac joints were seen with the two highest tofacitinib doses, while significant improvements in SPARCC spine scores were observed with all tofacitinib doses versus placebo. Patients with high baseline CRP (≥0.287 mg/dL—the upper limit of normal in the central laboratory) had a larger treatment effect with tofacitinib versus placebo than those with low baseline CRP (<0.287 mg/dL) [14].

A *post hoc* analysis of MRI scans from patients enrolled in the study showed a significant reduction in the total MRI inflammation score for the spine, as well as decreases in subscale

scores assessing inflammation of the vertebral bodies, posterior elements, corner and non-corner lesions, facet joints, and posterolateral inflammation. These reductions were statistically significant in the group receiving continuous TOFA therapy compared with placebo ($p < 0.0001$, except for the non-corner subscale, $p < 0.05$) at week 12. Assessments were performed using the "CANDEN MRI" scoring system [15].

In the randomized phase III trial, 269 adults were enrolled who met eligibility criteria similar to the phase II study; roughly four-fifths were bDMARD-naive, and about one-fifth had an inadequate response (IR) to ≤2 TNFi or had prior bDMARD (TNFi or non-TNFi) use without IR. Exclusion criteria included current or prior treatment with targeted synthetic disease-modifying antirheumatic drugs and current bDMARD treatment (prior bDMARD use was permitted if appropriately discontinued before randomization).

At the end of the double-blind period (1:1 randomization to tofacitinib 5 mg twice daily vs. placebo), at week 16, the ASAS20 response rate was significantly higher with tofacitinib (56.4%) than with placebo (29.4%; $p < 0.0001$). The ASAS40 response was also significantly higher with tofacitinib (40.6%) versus placebo (12.5%; $p < 0.0001$). Improvements were observed in ΔASDAS, ΔBASMI, and ΔFACIT-F, along with reductions in inflammation, in the tofacitinib group ($p \leq 0.05$ for tofacitinib 5 mg twice daily vs placebo per the prespecified step-down testing procedure for global type I error control).

By the end of the open-label phase (week 48), the continuous-tofacitinib group achieved ASAS20 and ASAS40 response rates of 65.4% and 50.4%, respectively; in the placebo→tofacitinib group the rates were 60.3% and 44.9%, respectively. Other response measures remained stable through study end. Significant differences favoring tofacitinib over placebo were seen as early as the first post-baseline visit (week 2) for ASAS20 and from week 4 for ASAS40. In the placebo→tofacitinib group, improvements were observed from week 16 [16].

Among patients receiving tofacitinib (TOFA), a greater reduction in fatigue was observed, reflected by improvements from baseline in the FACIT-F total score and BASDAI, as well as enhanced health-related quality of life, evidenced by better ASQoL and SF-36v2 PCS scores. TOFA treatment also had a positive effect on WPAI outcomes ($p < 0.001$), with the exception of the percentage of work time missed due to health problems.

Post hoc analysis of the referenced study demonstrated that the efficacy of tofacitinib exceeded that of placebo in bDMARD-naive and TNFi-IR patients at week 16 and was maintained through week 48. The absolute magnitude of responses was generally greater in bDMARD-naive patients versus TNFi-IR patients, whereas treatment discontinuation or dose reduction due to adverse events occurred more frequently in the TNFi-IR population [16,17].

The next *post hoc* analysis demonstrated that earlier initiation of TOFA was associated with faster improvement in the core domains of ankylosing spondylitis compared with delayed treatment. Based on study findings, approximately 50% of patients were likely to experience ≥30% improvement in pain and a ≥1.1-point reduction in ASDAS during the first month, ≥50% improvement in nocturnal pain and enthesitis by the second month, and improvement in morning stiffness by the third month [16,18].

Post hoc analyses of phase II and phase III clinical trials showed greater improvement with TOFA regardless of baseline CRP. Generally, the placebo-adjusted treatment effect for TOFA was numerically higher in the ≥5 mg/L and ≥10 mg/L baseline CRP subgroups than in the <5 mg/L or <10 mg/L subgroups across endpoints. In placebo patients receiving concomitant NSAIDs or sulfasalazine, CRP may have decreased, potentially confounding the true difference in CRP reduction with TOFA versus placebo. In the TOFA group, treatment-emergent adverse events (TEAEs) occurred more frequently among patients with low baseline CRP (<5 mg/L) [19].

It was shown that TOFA was more effective than placebo regardless of baseline BMI category. No differences in efficacy were observed between BMI categories, except in patients with BMI ≥30 kg/m², in whom the disease appeared more active or treatment-refractory; however, this subgroup was smaller in the study [20].

The effectiveness of tofacitinib was evaluated in a retrospective study of patients receiving combination therapy with TOFA plus bDMARDs after an inadequate response to bDMARD monotherapy. Fifteen adults had received at least one bDMARD for more than three months yet still failed to achieve an adequate response. Tofacitinib 5 mg twice daily was added to the existing regimen and continued for at least 12 weeks after initiation of combination therapy.

A significant reduction was observed in the overall ASDAS-CRP score, from a baseline of 3.82 ± 1.47 (2.83–4.99) to 1.47 ± 0.48 (0.75–2.44), with 46.7% of patients achieving remission, and 33.3% achieving low disease activity. The BASDAI score also improved, decreasing from a

baseline of 5.11 ± 1.42 (3.25–7.75) to 1.28 ± 0.70 (0.20–2.55). All tests reached statistical significance ($p < 0.05$) [21].

A comparative meta-analysis of the efficacy and safety of Janus kinase (JAK) inhibitors and secukinumab (an IL-17 monoclonal antibody) in ankylosing spondylitis, found that tofacitinib 5 mg was the most effective regimen for AS. Both JAK inhibitors and secukinumab were beneficial in patients with active disease who had an inadequate response to or intolerance of NSAIDs and were TNF-inhibitors–naive. There was no statistically significant difference in ASAS response rates between JAK inhibitors and secukinumab. In terms of safety, serious adverse event rates did not differ significantly across the seven treatment groups, indicating comparable safety profiles for JAK inhibitors, secukinumab, and placebo [22].

Safety of inhibitors

In the SELECT-AXIS 1 study, the most common adverse event in the upadacitinib group was asymptomatic elevation of creatine phosphokinase (CPK); four cases in the upadacitinib group and one in the placebo group were judged possibly related to the study drug. Other frequent adverse events included diarrhea and nasopharyngitis in both groups, and headache in the upadacitinib group. No serious infections, herpes zoster, malignancies, venous thromboembolic events, renal dysfunction, or deaths were reported [10].

In the 2-year extension, upadacitinib (UPA) was well tolerated, with a total exposure of 308.6 patient-years. The incidence of serious adverse events (SAEs) was 6.2 per 100 PY, and the incidence of adverse events leading to discontinuation was 5.5 per 100 PY. The three most common adverse events were nasopharyngitis, increased creatine phosphokinase (CPK), and upper respiratory tract infection. Serious AEs accounted for 19 of the 749 events reported. No new or previously unreported adverse events were observed [11].

In the studies presented, tofacitinib (TOFA) demonstrated a favorable safety profile. The most commonly reported treatment-emergent adverse events (TEAEs) were nasopharyngitis and upper respiratory tract infection. Serious adverse events in TOFA-treated patients were rare; in the 5 mg twice-daily group, a single serious infectious event-uveitis-was reported [14]. Up to week 48 of TOFA treatment, no deaths or cases of malignancy, major adverse cardiovascular events (MACE), thromboembolic events, gastrointestinal perforation, drug-induced liver

injury (DILI), opportunistic infections, or interstitial lung disease (ILD) were reported. Non-serious herpes zoster occurred in three (2.3%) patients [16].

General principles for the use of JAK inhibitors have been formulated for the ankylosing spondylitis (AS) population. They include excluding patients with ongoing opportunistic infections (chronic or acute), and patients ≥65 years, with cardiovascular risk factors if TNF-inhibitor therapy is a viable option. In line with EMA recommendations, tofacitinib may be used in such patients only when no suitable alternatives are available.

JAK inhibitors should also be avoided in patients with a malignancy within the previous 5 years and in those with severe hepatic impairment; in cases of severe renal impairment, the tofacitinib dose should be reduced to 5 mg once daily. Because data in pregnancy are insufficient, contraception is recommended for both women and men receiving JAK inhibitors, and the drug should be discontinued 4 weeks before a planned pregnancy [23].

The ORAL Surveillance study, which evaluated safety in patients aged ≥50 years with rheumatoid arthritis (RA) and cardiovascular risk factors, showed that safety events occurred significantly more frequently with tofacitinib than with TNF inhibitors (TNFi). Post hoc analyses of ORAL Surveillance identified subgroups with higher relative risk versus TNFi—namely patients aged ≥65 years, and/or long-term current or former smokers. In patients without these risk factors, no differences in risk between tofacitinib and TNFi were observed [24].

Studies have shown that use of JAK inhibitors is associated with a significantly higher risk of herpes zoster compared with placebo and active comparators (adalimumab or methotrexate), which may represent a class-specific effect. The risk of serious infections is similar to that observed with TNF-inhibitor biologics [25].

A meta-analysis by C. Bezzio of studies on tofacitinib in rheumatoid arthritis, ulcerative colitis, Crohn’s disease, psoriatic arthritis, and ankylosing spondylitis found no difference in overall cancer risk between tofacitinib and placebo or biologic therapies, but a slightly higher risk with tofacitinib compared with anti-TNF agents. Versus any control treatment, the relative risk (RR) for any malignancy was 1.06 (95% CI, 0.86 –1.31; p =0.95). In separate comparisons, there was no difference in overall cancer risk versus placebo (RR=1.04; 95% CI, 0.44–2.48; p =0.95) or versus biologics (RR=1.06; 95% CI, 0.86–1.31; p= 0.58). Compared with TNF inhibitors,

the overall RR for cancer was 1.40 (95% CI, 1.06–2.08; p =0.02). Similarly, statistically significant results were seen for "all cancers excluding nonmelanoma skin cancer" (RR=1.47; 95% CI, 1.05–2.06; p =0.03), whereas for nonmelanoma skin cancer alone the difference was not significant (RR=1.30; 95% CI, 0.22–5.83; p =0.88) [26].

Discussion

The studies presented indicate that upadacitinib 15 mg once daily and tofacitinib 5 mg twice daily are effective and safe treatment options for patients with ankylosing spondylitis (AS), particularly for those who do not tolerate NSAIDs or biologics or for whom such prior therapies were ineffective. These agents showed favorable effects on clinical symptoms of AS-such as pain, morning stiffness, fatigue, and inflammatory markers-as well as on patients' quality of life. Key advantages include oral administration (often easier and more comfortable for many patients than the injections used with biologic therapy) and a rapid onset of action.

The cited studies have limitations. The evidence base for JAK inhibitors in AS remains limited, and the sample sizes in the discussed trials may affect generalizability. Maximum follow-up was 2 years for upadacitinib and 48 weeks for tofacitinib. Further research is needed to assess long-term efficacy and safety, which is especially important for chronically treated patients. Future studies should also incorporate additional radiographic evaluation and examine specific subgroups, particularly those with prior inadequate response to bDMARDs.

Despite the promising therapeutic effects, JAK inhibitors carry defined risks, reflected in EMA and FDA recommendations. Their use requires an individualized benefit–risk assessment, especially in patients with additional risk factors. Moreover, all patients receiving JAK inhibitors should be closely monitored for both new and previously recognized treatment-related adverse reactions.

Conclusions

Studies have shown that tofacitinib and upadacitinib are effective and safe in the treatment of ankylosing spondylitis (AS), including in patients with an inadequate response to NSAIDs or bDMARDs. Both agents have a favorable benefit–risk profile and may be an effective treatment option in AS. Further research on long-term efficacy and safety is needed. For

patients for whom first-line therapy is ineffective or not tolerated, treatment with JAK inhibitors represents a promising therapeutic option.

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References

1. Păsăran, Emilia-Daniela, et al. “An Actual Insight into the Pathogenic Pathways of Ankylosing Spondylitis.” *Current Issues in Molecular Biology*, vol. 46, no. 11, 2024, pp. 12800–12812. https://doi.org/10.3390/cimb46110762.

2. Li, Hui, et al. “Clinical Trial Landscape for Ankylosing Spondylitis: Current Insights and Future Innovations.” *Pharmacological Research*, vol. 208, 2024, article 107365. https://doi.org/10.1016/j.phrs.2024.107365.

3. Akhondi, Hossein, and Matthew A. Varacallo. “Rheumatoid Arthritis and Ankylosing Spondylitis.” *StatPearls*, StatPearls Publishing, 4 Aug. 2023.

4. Nagit, Ruxandra-Elena, et al. “Exploring the Pathogenesis of Spondylarthritis beyond HLA-B27: A Descriptive Review.” *International Journal of Molecular Sciences*, vol. 25, no. 11, 2024, article 6081. https://doi.org/10.3390/ijms25116081.

5. Alihajdaraj, Rrezarta, et al. “Converging Pathways of Ankylosing Spondylitis and Rheumatic Fever: A Unique Case.” *Radiology Case Reports*, vol. 20, no. 1, 2024, pp. 91–96. https://doi.org/10.1016/j.radcr.2024.09.123.

6. Ren, Zheng, et al. “The Harmful Effect of Ankylosing Spondylitis on Diabetes Mellitus: New Evidence from Mendelian Randomization Analysis.” *Frontiers in Endocrinology*, vol. 15, 2024, article 1369466. https://doi.org/10.3389/fendo.2024.1369466.

7. Zhang, Ye, et al. “Genetic Associations in Ankylosing Spondylitis: Circulating Proteins as Drug Targets and Biomarkers.” *Frontiers in Immunology*, vol. 15, 2024, article 1394438. https://doi.org/10.3389/fimmu.2024.1394438.

8. Bilski, R., et al. “Environmental and Genetic Determinants of Ankylosing Spondylitis.” *International Journal of Molecular Sciences*, vol. 25, no. 14, 2024, article 7814. https://doi.org/10.3390/ijms25147814.

9. Gubar, E. E., et al. “Evaluation of the Possibility of Axial Psoriatic Arthritis Patients Meeting Classification Criteria for Axial Spondyloarthritis and Ankylosing Spondylitis.” *Doklady Biochemistry and Biophysics*, vol. 517, no. 1, 2024, pp. 173–181. https://doi.org/10.1134/S160767292470087X.

10. van der Heijde, Désirée, et al. “Efficacy and Safety of Upadacitinib in Patients with Active Ankylosing Spondylitis (SELECT-AXIS 1): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 2/3 Trial.” *The Lancet*, vol. 394, no. 10214, 2019, pp. 2108–2117. https://doi.org/10.1016/S0140-6736(19)32534-6.

11. van der Heijde, Désirée, et al. “Upadacitinib in Active Ankylosing Spondylitis: Results of the 2-Year, Double-Blind, Placebo-Controlled SELECT-AXIS 1 Study and Open-Label Extension.” *RMD Open*, vol. 8, no. 2, 2022, article e002280. https://doi.org/10.1136/rmdopen-2022-002280.

12. van der Heijde, Désirée, et al. “Efficacy and Safety of Upadacitinib for Active Ankylosing Spondylitis Refractory to Biological Therapy: A Double-Blind, Randomised, Placebo-Controlled Phase 3 Trial.” *Annals of the Rheumatic Diseases*, vol. 81, no. 11, 2022, pp. 1515–1523. https://doi.org/10.1136/ard-2022-222608.

13. Baraliakos, Xenofon, et al. “Efficacy and Safety of Upadacitinib in Patients with Active Ankylosing Spondylitis Refractory to Biologic Therapy: 2-Year Clinical and Radiographic Results from the Open-Label Extension of the SELECT-AXIS 2 Study.” *Arthritis Research & Therapy*, vol. 26, no. 1, 2024, article 197. https://doi.org/10.1186/s13075-024-03412-8.

14. van der Heijde, Désirée, et al. “Tofacitinib in Patients with Ankylosing Spondylitis: A Phase II, 16-Week, Randomised, Placebo-Controlled, Dose-Ranging Study.” *Annals of the Rheumatic Diseases*, vol. 76, no. 8, 2017, pp. 1340–1347. https://doi.org/10.1136/annrheumdis-2016-210322.

15. Østergaard, Mikkel, et al. “Tofacitinib Reduces Spinal Inflammation in Vertebral Bodies and Posterolateral Elements in Ankylosing Spondylitis: Results from a Phase 2 Trial.” *Rheumatology and Therapy*, vol. 10, no. 4, 2023, pp. 1001–1020. https://doi.org/10.1007/s40744-023-00564-y.

16. Deodhar, Atul, et al. “Tofacitinib for the Treatment of Ankylosing Spondylitis: A Phase III, Randomised, Double-Blind, Placebo-Controlled Study.” *Annals of the Rheumatic Diseases*, vol. 80, no. 8, 2021, pp. 1004–1013. https://doi.org/10.1136/annrheumdis-2020-219601.

17. Navarro-Compán, Victoria, et al. “Effect of Tofacitinib on Pain, Fatigue, Health-Related Quality of Life and Work Productivity in Patients with Active Ankylosing Spondylitis: Results from a Phase III Randomised, Double-Blind, Placebo-Controlled Trial.” *RMD Open*, vol. 8, no. 2, 2022, article e002253.

https://doi.org/10.1136/rmdopen-2022-002253.

18. Navarro-Compán, Victoria, et al. “Time to Improvement of Pain, Morning Stiffness, Fatigue, and Disease Activity in Patients with Ankylosing Spondylitis Treated with Tofacitinib: A Post Hoc Analysis.” *Arthritis Research & Therapy*, vol. 26, no. 1, 2024, article 105. https://doi.org/10.1186/s13075-024-03313-w.

19. Deodhar, Atul, et al. “Efficacy and Safety of Tofacitinib in Ankylosing Spondylitis by Baseline C-Reactive Protein Level: Post Hoc Analysis of Phase II and Phase III Clinical Trials.” *The Journal of Rheumatology*, vol. 51, no. 8, 2024, pp. 772–780. https://doi.org/10.3899/jrheum.2023-1198.

20. Norton, Hannah, et al. “Tofacitinib Efficacy/Safety in Patients with Ankylosing Spondylitis by Baseline Body Mass Index: A Post Hoc Analysis of Phase 2/3 Trials.” *Rheumatology and Therapy*, vol. 12, no. 1, 2025, pp. 67–84. https://doi.org/10.1007/s40744-024-00726-6.

21. Chang, Jing, and Guo Wang. “The Efficacy of Tofacitinib Combined with bDMARDs in the Treatment of Ankylosing Spondylitis Patients with Inadequate Response to bDMARDs: A Retrospective Study.” *BMC Rheumatology*, vol. 8, no. 1, 2024, article 3. https://doi.org/10.1186/s41927-024-00373-y.

22. Lee, Young Ho. “Comparative Efficacy and Safety of Janus Kinase Inhibitors and Secukinumab in Patients with Active Ankylosing Spondylitis: A Systematic Review and Meta-Analysis.” *Pharmacology*, vol. 107, nos. 11–12, 2022, pp. 537–544. https://doi.org/10.1159/000525627.

23. Nash, Philip, et al. “Points to Consider for the Treatment of Immune-Mediated Inflammatory Diseases with Janus Kinase Inhibitors: A Consensus Statement.” *Annals of the Rheumatic Diseases*, vol. 80, no. 1, 2021, pp. 71–87. https://doi.org/10.1136/annrheumdis-2020-218398.

24. Kristensen, Lars Erik, et al. “Risk Stratification of Patients with Psoriatic Arthritis and Ankylosing Spondylitis for Treatment with Tofacitinib: A Review of Current Clinical Data.” *Rheumatology and Therapy*, vol. 11, no. 3, 2024, pp. 487–499. https://doi.org/10.1007/s40744-024-00662-5.

25. Singh, Jasvinder A. “The Emerging Safety Profile of JAK Inhibitors in Rheumatic Diseases.” *BioDrugs*, vol. 37, no. 5, 2023, pp. 625–635. https://doi.org/10.1007/s40259-023-00612-7.

26. Bezzio, Carlo, et al. “Cancer Risk in Patients Treated with the JAK Inhibitor Tofacitinib: Systematic Review and Meta-Analysis.” *Cancers (Basel)*, vol. 15, no. 8, 2023, article 2197. https://doi.org/10.3390/cancers15082197.