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CASE SERIES & REVIEW

Upadacitinib for the treatment of radiographic axial spondyloarthritis — case series and review of the literature

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Abstract

Upadacitinib is a Janus kinase (JAK) inhibitor approved for the treatment of different rheumatic diseases, including axial spondyloarthritis (axSpA). In phase III clinical trials, upadacitinib was associated with rapid and significant improvement in disease parameters, including scores for pain, function and mobility, signs of structural damage, and patient-reported outcomes, and had an overall incidence of adverse events similar to that in the placebo group. Improvement in axSpA disease severity was observed in both biologic-naive patients and those with prior biologic exposure, and this improvement was sustained during open-label treatment. Indirect comparisons with other agents suggest that upadacitinib is more effective than biologics and other JAK inhibitors in patients with axSpA and is associated with the lowest number-needed-to-treat. Long-term safety data indicate that upadacitinib is well tolerated in patients with axSpA, with a low rate of infections, malignancies, major adverse cardiovascular events and thromboembolism. Four case studies described here illustrate the effectiveness of upadacitinib in a range of real-world patients with axSpA, including patients with early disease and those who have been pre-treated with biologics.

Keywords: ankylosing spondylitis, axial spondyloarthritis, JAK inhibitors, upadacitinib.

Citation

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Introduction

The term axial spondyloarthritis (axSpA) is used to describe chronic inflammatory conditions affecting the axial skeleton that mainly involve the sacroiliac joints (SIJs) and spine.[1] Patients with axSpA experience chronic back pain with an insidious onset usually at a young age (<45 years).[1] The pain is often worse at night and eased by walking but not by rest.[1] In Italy, axSpA affects about 1 in 100 people, with an estimated prevalence of 1.06%.[2]

axSpA is further categorized into non-radiographic or radiographic forms with the latter characterized by evidence of sacroiliitis on imaging.[3] Non-radiographic axSpA is usually considered an early form of the disease prior to the development of overt structural damage.

The goal of treatment for axSpA is to maximize the patient's quality of life by controlling symptoms and inflammation, preventing progressive structural damage, and preserving function and participation in daily life.[4] Major guidelines from the USA and Europe recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs) as first-line therapy and local glucocorticoid injections.[4,5] Disease-modifying antirheumatic drugs (DMARDs) are recommended to suppress active axSpA; however, conventional synthetic DMARDs (such as sulfasalazine and methotrexate (MTX)) should be reserved exclusively for patients who also present with peripheral involvement.[4,5]

The 2022 guidelines from the Assessment of Spondyloarthritis International Society (ASAS) and European Alliance of Associations for Rheumatology (EULAR) state that treatment with a tumour necrosis factor (TNF) inhibitor, IL-17 inhibitor or Janus kinase (JAK) inhibitor (JAKi) is appropriate for patients after failure of conventional therapy; treatment intensification should be considered for patients with persistently high disease activity.[4]

Patients who achieve sustained remission should stay on therapy; for those who do not achieve sustained remission or relapse, ASAS-EULAR guidelines recommend switching to a different biologic or JAKi.[4]

JAKis are small-molecule inhibitors targeting intracellular JAK enzymes, which play a critical role in mediating the transcription of cytokine receptors.[6] Whilst first-generation, non-selective JAKis were initially approved in the USA between 2012 and 2017,[6] the second-generation JAKi upadacitinib marked a significant advancement. Approved in 2019 for the treatment of active rheumatoid arthritis in both Europe and the USA, upadacitinib was the first second-generation JAKi to gain regulatory approval.[7,8] Since then, its indications have broadened to include psoriatic arthritis (PsA), ulcerative colitis, atopic dermatitis, and both radiographic and non-radiographic forms of axSpA.

This article reviews the relevant literature regarding the efficacy and safety of upadacitinib in the treatment of active radiographic axSpA and presents a series of four case studies in which upadacitinib was used for this indication.

Methods

A research of published literature in the PubMed database was undertaken on 17 October 2024 to identify studies with "upadacitinib" AND ("spondylit*" OR "spondyloarthrit*") in the title or abstract. No date limits or language limits were set. The abstracts were manually reviewed for relevant clinical trials, observational studies or meta-analyses, in which upadacitinib was used to treat radiographic axSpA. Relevant patient cases were identified by the authors and de-identified to ensure confidentiality. The description of each case follows CARE guidelines,[9] where applicable.

Review

Upadacitinib pharmacology

JAKs are a group of four intracellular enzymes (JAK1, JAK2, JAK3 and TYK2) involved in the JAK–STAT intracellular signalling pathway, which rapidly transmits extracellular signals to the nucleus to regulate the biological response.[10] More than 50 cytokines are involved in JAK–STAT signalling, mediating cell differentiation and immune response,[10] with different cytokines activating different JAKs.[11] Binding of a ligand to the relevant receptor activates this pathway, in which JAKs phosphorylate STAT and STATs enter the nucleus where they regulate gene transcription.[10] The JAK–STAT pathway is activated in a number of inflammatory conditions, including spondyloarthritis (SpA).[10]

Inflammation in SpA is driven by a number of key cytokines, mainly TNF, and IL-2, IL-6, IL-10, IL-15, IL-17 and IL-23,[11] some of which interact with the JAK–STAT pathway. JAK1 is activated by IL-2, IL-15, IL-6 and interferon, amongst other cytokines, and upadacitinib is selective for JAK1.[9,11] Biomarker analyses have demonstrated that upadacitinib directly inhibits a range of JAK1-dependent cytokine pathways (including interferon, IL-6, IL-2, IL-5 and IL-7), and indirectly inhibits several JAK1-independent pathways (IL-1, IL-23, IL-17, IL-18 and TNF) as well as other JAK-dependent cytokines such as granulocyte–monocyte colony-stimulating factor.[12] The result is inhibition of a number of key functional pathways, such as leukocyte activation and migration, inflammatory responses, and the pathogenic processes that lead to connective tissue damage.[12]

Efficacy of upadacitinib in axSpA

Registration trials for upadacitinib in axSpA were the phase III multicentre, randomized, placebo-controlled SELECT-AXIS 1 and 2 studies (Table 1).[13,14] SELECT-AXIS 1 was conducted in 187 patients who had not previously received biologic therapy,[14] whereas SELECT-AXIS 2 was in 420 patients who had progressed after previous treatment with a biologic.[13] The primary end point of both studies was the proportion of patients with at least 40% improvement in ASAS response criteria (ASAS40) at week 14.

In both studies, the primary end point data significantly favoured upadacitinib over placebo, with 52% of patients achieving ASAS40 at week 14 in the upadacitinib group compared to 26% of patients in the placebo group in SELECT-AXIS 1 (p=0.0003)[14] and 45% *versus* 18%, respectively, in SELECT-AXIS 2 (p<0.0001).[13]

In both studies, significant improvements compared to placebo were also seen in a range of secondary end points at week 14, including the proportion of patients achieving 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50) and ASAS partial remission, and scores for Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Functional Index (BASFI), and Spondylitis Research Consortium of Canada (SPARCC) MRI Spine Index.[13,14] In SELECT-AXIS 2, significant improvements *versus* placebo were also seen in the proportion of patients achieving ASAS20, and in scores for ASDAS with C-reactive protein (ASDAS-CRP), Bath Ankylosing Spondylitis Metrology Index (BASMI), and Maastricht Ankylosing Spondylitis Enthesitis (MASES), SPARCC MRI SIJ Index, and ASAS Health Index.[13]

Assessment of patient-reported outcomes in SELECT-AXIS 2 showed that upadacitinib was associated with a rapid and clinically significant improvement in patient global assessment, fatigue (measured using the Functional Assessment

Table 1. Design and outcomes of the phase 3 SELECT AXIS 1 and 2 studies in patients with AxSpA.

Reference	Design	Patients	*N*	Duration (weeks)	Efficacy	Adverse events
SELECT AXIS 1[13]	MC, R, DB, PC	Biologic-naive active[a] axSpA with inadequate response to ≥2 NSAIDs (or intolerance or contraindication to NSAIDs); 71% male; mean 45.4 years	187	14	**Primary end point:** ASAS40: 52% *vs* 26% with Upa *vs* placebo (p=0.0003) **Secondary end points:** Significantly better ASDAS, SPARCC MRI spine and SIJ, BASFI and ASA Health Index scores with Upa *vs* placebo Higher proportion of patients with ASAS20, BASDAI50, ASAS partial remission, ASDAS LDA, ASDAS inactive disease, ASDAS clinically important or major improvement with Upa *vs* placebo	AEs in 55% of placebo patients *vs* 62% of Upa patients Serious AEs in 1% *vs* 1% Infections in 28% placebo patients *vs* 20% Upa patients
SELECT AXIS 2[12]	MC, R, DB, PC	Active[a] axSpA with inadequate response to biologic therapy; 74% male; mean 42.4 years	420	14	**Primary end point:** ASAS40: 45% *vs* 18% with Upa *vs* placebo (p<0.0001) **Secondary end points:** Significantly better improvements in ASDAS, total and nocturnal back pain, SPARCC MRI spine and SIJ, BASFI, ASQoL, ASAS Health Index, BASMI and MASES scores with Upa *vs* placebo Higher proportion of patients with ASAS20, BASDAI50, ASAS partial remission, ASDAS LDA, ASDAS inactive disease, with Upa *vs* placebo	AEs in 37% of placebo patients *vs* 41% of Upa patients Serious AEs in 0.5% *vs* 2.8% with placebo *vs* Upa Infections in 12.9% placebo patients *vs* 14.7% Upa patients

[a]BASDAI score ≥4 and patient assessment of back pain ≥4 at screening.
AE, adverse event; ASAS 20 or 40, assessment of SpondyloArthritis international Society 20 or 40 response; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; axSpA, axial spondyloarthritis; BASDAI50, ≥50% improvement from baseline in Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; DB, double-blind; LDA, low disease activity; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MC, multicentre; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; PC, placebo controlled; R, randomized; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada; Upa, upadacitinib.

of Chronic Illness Therapy–Fatigue scale), physical function (measured using the BASFI), and health-related quality of life (measured using the ASAS Health Index, Ankylosing Spondylitis Quality of Life and Short Form-36), and work productivity (measured using the Work Productivity and Activity Impairment questionnaire).[15] The proportion of patients achieving the minimum clinically important difference was higher in the upadacitinib than the placebo group for all of the measured patient-reported outcomes.[15] Patients also experienced a significant reduction in the severity of total back pain and nocturnal back pain compared to placebo (p<0.0001), with an average reduction in pain score of at least 3 points on a 0–10 numerical rating scale.[13]

The SELECT studies included an open-label extension (OLE) for patients who completed the 14-week double-blind phase.[16,17] All patients entering the OLE of SELECT-AXIS 1 (n=178) received upadacitinib 15 mg/day for 90 weeks. The proportion of patients who achieved ASAS40 continued to increase through week 40 amongst the group initially randomized to upadacitinib, reaching 66% and remaining stable at that level through week 104.[16,17] A similar pattern of ongoing improvement was seen with secondary end points of ASAS partial remission, ASAS low disease activity (LDA) and ASAS inactive disease. After switching to upadacitinib, patients who had originally been randomized to placebo had a similar response to those in the original upadacitinib group, with rapid improvement in primary and secondary end points. At week 104, the two groups had comparable rates of ASAS40, ASAS patient remission, ASDAS LDA and inactive disease and BASDAI50.[16] The same pattern of response was seen for change from baseline in other end points, including ASDAS score, BASFI, pain end points, quality of life parameters, spinal mobility, measures of enthesitis and peripheral manifestations, and MRI parameters.[16]

Pain is a sentinel symptom of axSpA, and is rated by patients as the most important aspect of their health.[18]

A likely reason for its importance to patients is the major effect pain has on patients' ability to engage in regular activities, and the negative impact it has on relationships, mood, self-esteem and quality of life.[19,20] As described earlier, upadacitinib significantly reduced back pain in the SELECT-AXIS 2 study.[13] A *post hoc* analysis of data from SELECT-AXIS 1 also showed rapid and significant reductions in pain end points, within 2 weeks of starting upadacitinib, that were sustained over 12 months of treatment.[21] At 12 months, 76%, 72% and 54% of patients receiving upadacitinib had a reduction in pain by ≥30%, ≥50% or ≥70%, respectively, compared to baseline.[21]

The significant benefits of upadacitinib compared to placebo in patients with axSpA have been confirmed in subsequent meta-analyses, including data from randomized controlled trials.[22–24]

Currently, there are no head-to-head studies comparing JAKi with other biologic agents in patients with axSpA. Network meta-analyses that indirectly compared the effects of upadacitinib with other advanced therapies (biologics and other JAKis) have produced mixed results.[25–27] One reported that tofacitinib had the highest likelihood and upadacitinib had the second highest likelihood of being the best JAKi for achieving ASAS40 response.[26] Two other network meta-analyses found that upadacitinib had the highest rate of ASAS40 response compared to the other agents in each analysis in patients who were biologic naive or experienced,[27] and the highest rate of ASDAS LDA in patients who were TNF inhibitor naive or experienced.[25] Where calculations could be made on the number needed to treat to achieve the specified outcomes in one patient, the number needed to treat was consistently lowest with upadacitinib.[25,27]

Persistence with treatment in the real world may be a marker of efficacy or tolerability, and real-world comparative studies report mixed results. The BIOBADASER 3.0 registry found a similar rate of persistence with TNF inhibitors and JAKis in patients with SpA,[28] whereas the German RHADAR registry found that patients with axSpA taking JAKis were more likely to discontinue treatment than patients taking TNF inhibitors or IL-17 inhibitors.[29] The primary reason for discontinuation in the RHADAR study was primary non-response.[29] However, patients receiving JAKis had more severe disease and had taken more previous medications than patients in the TNF inhibitor group,[29] and both baseline disease severity and receipt of multiple lines of previous treatment are risk factors for biologic discontinuation.[28]

Safety of upadacitinib in axSpA

An integrated analysis of safety data from upadacitinib clinical trials in patients with radiographic axSpA found a low overall rate of treatment-related adverse events (AEs) (188.3 per 100 patient-years (PY)) and serious treatment-related AEs (8.2 per 100 PY).[30] The most common AEs in this analysis were COVID-19 (9.4 events per 100 PY), nasopharyngitis (8.6 events per 100 PY) and upper respiratory tract infection (5.9 events per 100 PY),[30] whereas in the SELECT AXIS 1 and 2 studies, the most common AEs with upadacitinib were enzyme elevations (creatine phosphokinase, alanine aminotransferase or aspartate aminotransferase) but these were usually asymptomatic and reversible.[14,16] The integrated analysis reported only one death (by suicide) in a patient with axSpA during treatment with upadacitinib, and most deaths in patients receiving upadacitinib for other indications (mostly PsA) were related to COVID-19.[30]

During long-term use of upadacitinib in SELECT-AXIS 1 and its OLE, the most common AEs were nasopharyngitis (which occurred at a rate of 14.9 per 100 PY), increased blood creatine phosphokinase levels (11.3 per 100 PY) and upper respiratory tract infection (9.1 per 100 PY).[16]

Specific safety concerns with long-term use of potent anti-inflammatory therapy, such as biologics or JAKis, include infections, malignancies, major adverse cardiovascular events (MACE) and venous thromboembolism.[31,32] Long-term analyses of data with upadacitinib show low rates of these events in patients with axSpA (Table 2),[30,33] and no increased risk of cancer or MACE relative to TNF inhibitors in patients with axSpA.[28,34]

In clinical trials with upadacitinib, the rates of MACE and venous thromboembolism were generally low in patients with axSpA, and lower than in patients with PsA or rheumatoid arthritis.[35] A separate network meta-analysis including a range of JAKis found that the incidence of cancer was similar in patients receiving a JAKi or a placebo, whereas patients receiving a TNF inhibitor had a lower incidence of cancer compared to placebo.[36]

Compared to other biologics (IL-17or TNF inhibitors), JAKis are associated with an increased risk of herpes zoster reactivation,[34] and patients starting these treatments are advised to get two doses of the recombinant herpes zoster vaccine.[37]

Case reports

Case 1

A 47-year-old man with a long history of smoking was diagnosed with SpA in 2008, presenting with significant peripheral joint involvement, including arthritis in the knees, hands and ankles, and HLA-B27 positivity. Initial treatments included NSAIDs, joint aspirations and local

Table 2. Integrated safety analysis of data from clinical trials with upadacitinib 15 mg/day in patients with axSpA and up to 5 years of follow-up.[27]

Type of AE	Adverse events per 100 patient-years (95% CI)		
	Radiographic AxSpA (*n*=596)	Non-radiographic AxSpA (*n*=286)	Any AxSpA (*n*=882)
Any AE	185.9 (117.3–194.9)	195.1 (180.2–211.0)	188.3 (180.8–196.0)
Any serious AE	8.1 (6.4–10.1)	8.6 (5.7–12.5)	8.2 (6.7–10.0)
Discontinuation due to AE	3.7 (2.6–5.2)	5.2 (3.1–8.4)	4.1 (3.1–5.4)
Deaths	0.1 (0.0–0.6)	0	0.1 (0.0–0.4)
Infections			
Serious infection (including COVID-19)	2.6 (1.6–3.8)	0.9 (0.2–2.7)	2.1 (1.4–3.1)
Serious infection (excluding COVID-19)	1.1 (0.5–2.0)	0.3 (0.0–1.7)	0.9 (0.4–1.6)
Herpes zoster	2.8 (1.8–4.1)	1.9 (0.7–4.0)	2.5 (1.7–3.6)
Active tuberculosis	0	0	0
Laboratory AEs			
Hepatic enzyme elevation	8.6 (6.8–10.7)	5.9 (3.5–9.2)	7.9 (6.4–9.6)
CPK elevation	3.8 (2.7–5.3)	NR	NR
Anaemia	1.7 (1.0–2.8)	0.9 (0.2–2.7)	1.5 (0.9–2.3)
Neutropenia	3.3 (2.2–4.7)	3.4 (1.7–6.1)	3.3 (2.4–4.5)
Lymphopenia	0.6 (0.2–1.4)	0	0.5 (0.2–1.0)
Cancer			
Malignancies (excluding NMSC)	0.2 (0.0–0.8)	0.3 (0.0–1.7)	0.2 (0.0–0.7)
NMSC	0.2 (0.0–0.8)	0.3 (0.0–1.7)	0.2 (0.0–0.7)
Lymphoma	0.1 (0.0–0.6)	0.3 (0.0–1.7)	0.2 (0.0–0.6)
Cardiovascular events			
MACE (adjudicated)	0.1 (0.0–0.6)	0.3 (0.0–1.7)	0.2 (0.0–0.6)
VTE (adjudicated)	0.3 (0.1–0.9)	0.6 (0.1–2.2)	0.5 (0.2–1.0)

AE, adverse event; AxSpA, axial spondyloarthritis; CPK, creatine phosphokinase; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; VTE, venous thromboembolism.

steroid injections, which provided only temporary relief. Since the disease predominantly affected peripheral joints, he was started on a sequence of conventional DMARDs, including leflunomide, sulfasalazine and MTX, but none proved effective.

In 2010, the patient developed inflammatory back pain, prompting further investigation. MRI of the pelvis revealed significant inflammation of the SIJs, and X-rays confirmed bilateral grade II sacroiliitis, consistent with radiographic axSpA.

In 2011, the patient began combination therapy with etanercept and MTX, but the treatment was discontinued after 3 months due to lack of efficacy. He was also diagnosed with hyperuricaemia and started on allopurinol during this time. In 2012, adalimumab monotherapy was introduced, and the patient experienced significant symptom improvement. Within 4 months, his ASDAS-CRP score dropped from 3.7 to 1.5, indicating a substantial reduction in disease activity. This response was maintained for several years with stable disease control.

However, in 2017, the patient experienced a severe flare-up, characterized by worsening low back pain and new-onset hip pain. MRI revealed multiple disc protrusions and significant hip joint effusion. Therapy was

switched to the IL-17A inhibitor secukinumab but, within 2 months, symptoms worsened, including swelling in the left knee. Additional treatments, including sulfasalazine and the reintroduction of MTX, were unsuccessful in controlling disease activity.

In 2018, following months of uncontrolled symptoms and persistent corticosteroid dependence, the patient was switched to golimumab. Although he experienced some relief, daily corticosteroids (prednisone >12.5 mg/day) were still required. His situation was further complicated by a serious ST-elevation myocardial infarction with ventricular fibrillation, necessitating urgent intervention. Given his cardiovascular risks, minimizing corticosteroid use became a priority.

Despite various interventions, the disease remained difficult to manage, with recurrent episodes of syncope requiring the implantation of a loop recorder in 2019. After multiple treatments had failed, ixekizumab, another IL-17 inhibitor, was tried but proved ineffective after 6 months.

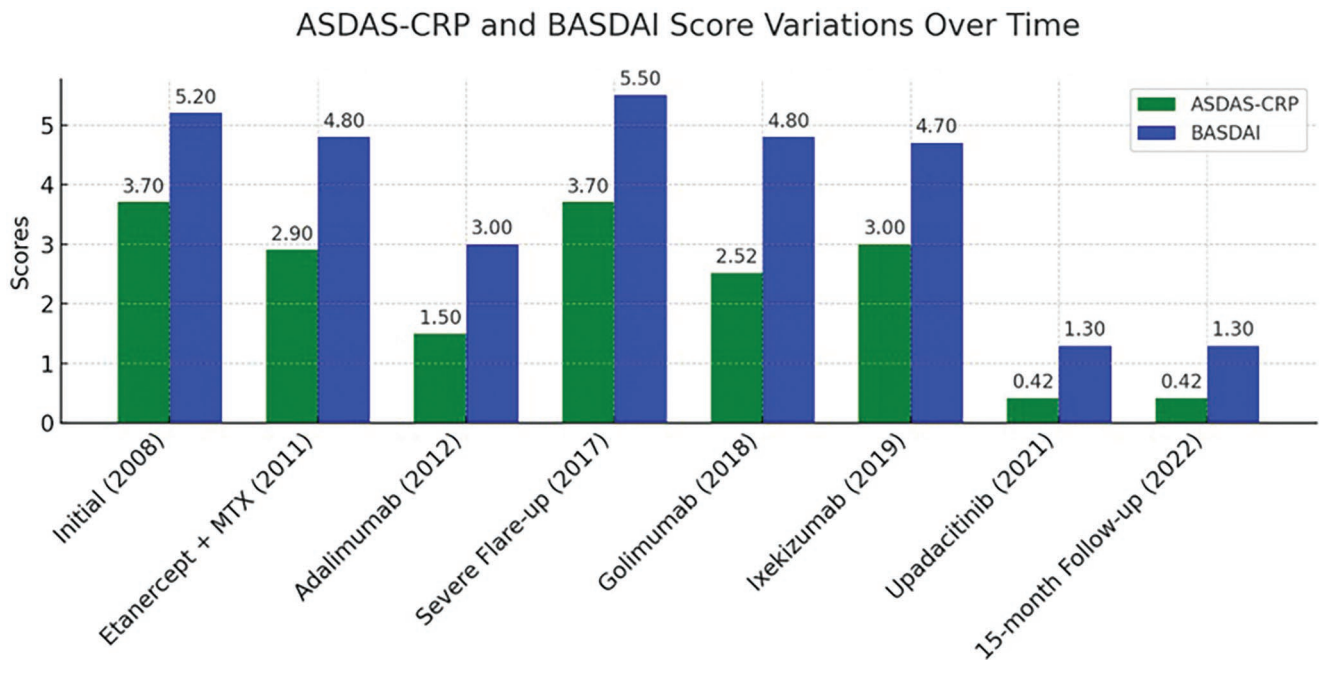
By 2021, with limited options remaining and a complex clinical picture, the patient began treatment with upadacitinib, despite the potential cardiovascular risks. Remarkably, within 3 months of starting upadacitinib, he experienced significant improvement. His corticosteroid dose was reduced to 4 mg/day, and disease activity scores showed substantial improvement: ASDAS-CRP dropped from 2.52 to 0.42, BASDAI from 4.17 to 1.3, and DAPSA for peripheral involvement improved to 1.2.

At the 15-month follow-up, the patient showed sustained clinical response on upadacitinib, maintaining effective disease control and reducing corticosteroid dependency, though tapering below 4 mg/day was not achieved. This case underscores the complexities of managing radiographic axSpA with significant peripheral involvement, especially in a patient with multiple failed treatments and comorbidities. Upadacitinib emerged as a highly effective treatment option, providing substantial relief where other therapies had failed. Despite the cardiovascular risks, the patient achieved and maintained satisfactory disease control on upadacitinib. ASDAS-CRP and BASDAI variations over time in response to treatment in this patient with radiographic axSpA are depicted in Figure 1.

Case 2

A 59-year-old non-smoking female, with no significant comorbidities, was initially diagnosed with PsA 20 years previously. Eight years ago, she presented to our rheumatology unit, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), with cutaneous psoriasis localized to the extensor surfaces of her elbows (PASI 0.2), accompanied by joint pain in both hands and feet, as well as swelling of the interphalangeal joints. Her symptoms were refractory to MTX, and other therapies, including sulfasalazine and leflunomide, had been discontinued due to adverse reactions (skin rash and hypertension, respectively). The patient also reported the onset of

Figure 1. Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score over time in Case 1.



inflammatory back pain. Clinimetric assessments revealed high disease activity, with an ASDAS-CRP score of 2.64 and a DAPSA score of 42.59.

Pelvic MRI revealed bone marrow oedema, indicative of osteitis, in the lower third of the left SIJ, extending into both the sacral and iliac regions. X-ray imaging confirmed sacroiliitis, graded as 2 on the right side and 3 on the left, therefore fulfilling the New York modified classification criteria for ankylosing spondylitis.[38] HLA-B27 testing was negative. Based on these clinical and radiological findings, the patient was diagnosed with radiographic axSpA with concomitant psoriasis.

Given the axial involvement and refractoriness of peripheral joint involvement to prior therapies, the anti-TNF monoclonal antibody golimumab was initiated, along with a daily dose of 10 mg prednisone.

At the 3-month follow-up, the patient reported significant improvement in cutaneous involvement (PASI 0) and peripheral arthritis (DAPSA 19.1 – moderate disease activity). However, axial symptoms showed only modest improvement; ASDAS-CRP had decreased to 2.3, indicating persistently high disease activity. Further improvement was observed following a 1-month course of NSAIDs, reducing ASDAS-CRP to 1.6 (low disease activity).

The patient's clinical status remained stable until 2020, when she experienced exacerbations in both peripheral joints (DAPSA 47.2 – high disease activity) and the axial skeleton (ASDAS-CRP 3.87 – very high disease activity), though her skin condition remained controlled (PASI 0).

Due to worsening symptoms, golimumab was discontinued, and treatment with the anti-IL-17A monoclonal antibody secukinumab was initiated, in combination with a daily dose of prednisone 12.5 mg. However, after 4 months of secukinumab treatment, there was no clinical improvement, and a slight worsening was observed (DAPSA 51.2, ASDAS-CRP 3.90).

The treatment regimen was then changed to intravenous infliximab at a dose of 5 mg/kg every 8 weeks. This resulted in significant improvements in both peripheral and axial manifestations, with DAPSA reducing to 13.16 and ASDAS-CRP to 1.2. Disease control was sustained over the following 2 years and the patient successfully discontinued corticosteroid use.

By the third year of infliximab treatment, the patient began experiencing recurrent episodes of joint and buttock pain, which were managed with increasingly frequent short courses of corticosteroids and NSAIDs. In December 2023, she experienced a significant disease flare, with DAPSA rising to 58.26 (high disease activity) and ASDAS-CRP increasing to 3.8 (very high disease activity). Laboratory tests revealed elevated inflammatory markers, including an erythrocyte sedimentation rate (ESR) of 112 mm/h and CRP of 4.9 mg/dL. Additionally, for the first time since her initial presentation, her skin condition had worsened (PASI 1.2).

In response to this flare, infliximab was discontinued, and treatment with the JAK1-selective inhibitor upadacitinib 15 mg/day was started. Within 3 months of starting upadacitinib, the patient experienced marked clinical improvement across all disease domains, with reductions in DAPSA (to 16.17) and ASDAS-CRP (to 1.9), and complete resolution of cutaneous lesions (PASI 0). Corticosteroids and NSAIDs were also discontinued. At the most recent follow-up, 7 months after initiating upadacitinib, the patient had achieved complete remission, with a DAPSA score of 2.02, ASDAS-CRP of 0.59 and PASI of 0. Laboratory investigations confirmed this disease control, with CRP at 0.2 mg/dL and ESR at 10 mm/h.

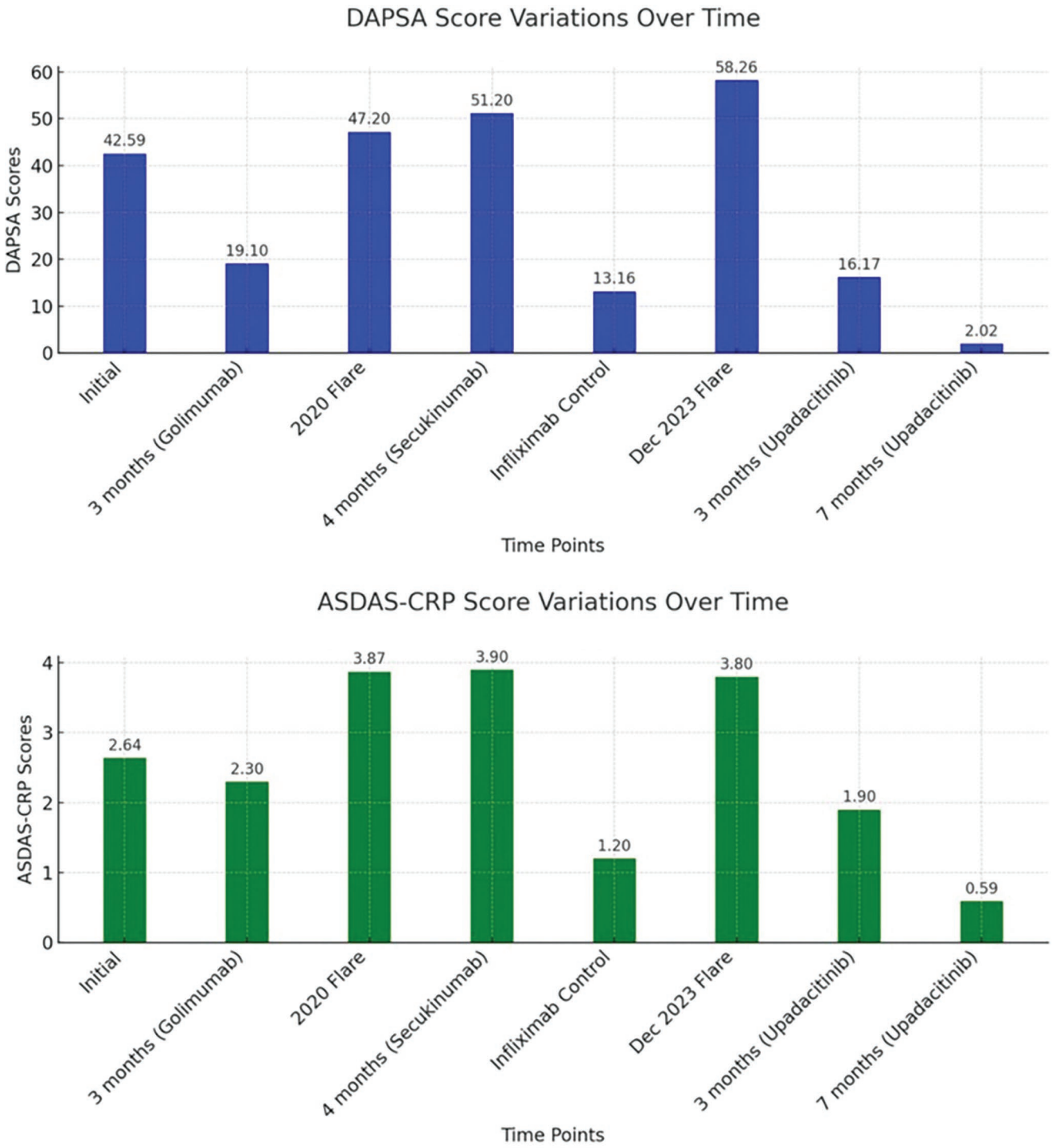
This case highlights the complexity of managing radiographic axSpA, particularly in patients who have demonstrated inadequate response to multiple prior biologic therapies, including anti-TNF and anti-IL17 agents. Upadacitinib demonstrated substantial effectiveness in this difficult-to-treat case, achieving remission and comprehensive disease control where previous biologics had failed. Variations in DAPSA and ASDAS-CRP scores over time in relation to treatment changes are depicted in Figure 2.

Case 3

A 56-year-old male was referred to our Rheumatology, Allergology and Clinical Immunology unit, Department of Systems Medicine, because of a 6-month history of low back pain, stiffness with limited activity, and peripheral arthralgias affecting the hands and shoulders. He had taken NSAIDs with partial symptom improvement. He had no comorbidities, no history of trauma, skin or nail psoriasis, uveitis, other joint pains, arthritis, inflammatory bowel disease or other connective tissue disorders. During clinical examination, the patient had pain in the SIJs (score of 7 out of 10), positive FABER (flexion, abduction and external rotation) test, but negative Wasserman and Lasègue tests. Spine mobility was preserved, and the Schober test and BASMI were normal. In addition, the patient had arthritis in his left knee and enthesitis of both Achilles tendons.

Laboratory tests showed normal haematology and biochemistry but elevated CRP levels (5.2 mg/dL; nor-

Figure 2. Disease Activity in Psoriatic Arthritis (DAPSA) score and Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) over time in Case 2.



mal range: 0–0.5) and ESR (21 mm/first hour; normal range: 0–25). HLA-B27 was negative.

Pelvic MRI using T1-weighted fat-suppressed images revealed hyperintense lesions in both SIJs, which were interpreted as oedema, and initial irregularities of the bone cortex (Figure 3A). No spinal abnormalities were detected on MRI. X-ray revealed bilateral stage 2 sacroiliitis.

Based on ASAS criteria,[3] a diagnosis of radiographic axSpA was made and treatment was initiated with NSAIDs, sulfasalazine and the TNF inhibitor etanercept subcutaneously (SC) 50 mg/week.

After 1 year of treatment, the patient reported no improvement in pain or morning stiffness. Moreover, he experienced migratory arthritis in the knee and ankle joints. Blood tests showed persistently elevated CRP

(6.5 mg/dL). BASDAI score was 5.7 and ASDAS-CRP 4.84, and the disease was considered active. Repeat MRI of the SIJs showed a progression of inflammation, with bone marrow oedema and erosions (Figure 3B). Given the active axSpA and the lack of success with his previous medical intervention, we discontinued etanercept and started upadacitinib 15 mg/day.

A month after starting upadacitinib, the patient reported a marked improvement in axial and peripheral pain. At the 3-month follow-up, the patient was no longer experiencing arthritis, low back pain or morning stiffness, ESR was 2 mm/first hour and CRP was 0.4 mg/dL. ASDAS-CRP was 1.88 and BASDAI score was 3.3, suggesting LDA. The patient continued upadacitinib and achieved clinical/biochemical and imaging remission a year later (Figure 3C).

Case 4

A 46-year-old woman had been diagnosed 10 years previously with radiographic axSpA in accordance with the ASAS and modified New York criteria.[3,38] The patient and her family had no history of psoriasis, gastroenteric manifestations or recent genitourinary infections. However, she had the following comorbidities: essential hypertension, bullous pemphigoid, obesity class I (body mass index (BMI) 33.9 kg/m^2) and fibromyalgia.

At diagnosis, she presented with low back pain associated with enthesitic peripheral involvement (bilateral plantar talalgia). MRI demonstrated inflammation in both SIJs, and x-ray revealed stage 3 sacroiliitis on the right (Figure 4). She was negative for HLA-B27 antigen. axSpA was active with a BASDAI score of 7.9 and an ASDAS-CRP score of 3.67. The patient was treated with SC etanercept 50 mg/week and NSAIDs, leading to initial symptomatic improvement.

Her symptoms remained stable throughout the following years until February 2020, when the patient experienced hand flexor tenosynovitis, epicondylitis and elbow arthritis. Elbow ultrasound showed lateral epicondylitis, prompting initiation of SC MTX 15 mg/week, but it was stopped due to intolerance.

Etanercept was switched to golimumab. However, there was no improvement in the patient's disease activity, and she had recurrence of moderate disease activity (possibly due to high BMI), so the anti-IL-17 agent secukinumab was started. Unfortunately, secukinumab was only partially and temporarily effective, with recurrent episodes of cervical and low back pain at night, morning stiffness lasting 1 hour every day, and an increase in inflammatory markers. In addition, the patient experienced widespread arthromyalgia, insomnia and mild depression.

Considering the failure of both TNF inhibitors and IL-17 inhibitors and the patient's BMI, age, and low

Figure 3. Magnetic resonance imaging using T1-weighted image (on the left) and short tau inversion recovery (on the right) of the sacroiliac joints in a patient with radiographic axial spondyloarthritis (case 3). (A) At the time of diagnosis; (B) After 1 year of treatment with etanercept, sulfasalazine and non-steroidal anti-inflammatory drugs, prompting the initiation of upadacitinib. (C) After 1 year of upadacitinib. No bone marrow oedema is seen in the short tau inversion recovery sequence.

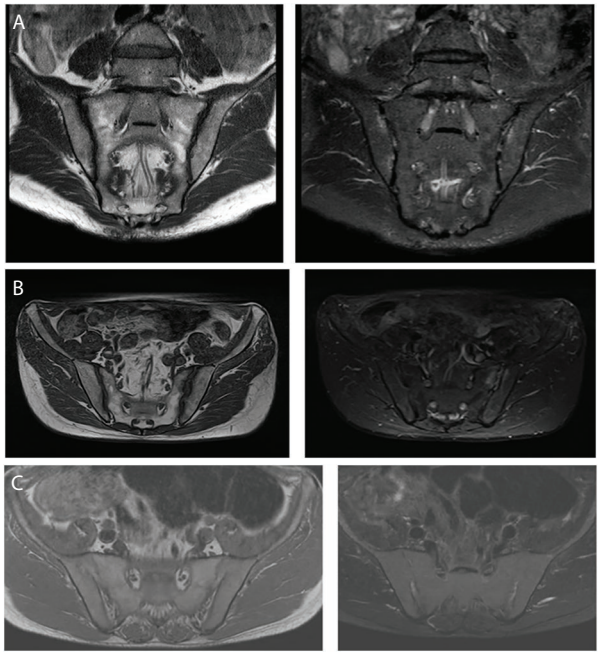


Figure 4. X-ray showing stage 3 sacroiliitis on the right side in case 4.

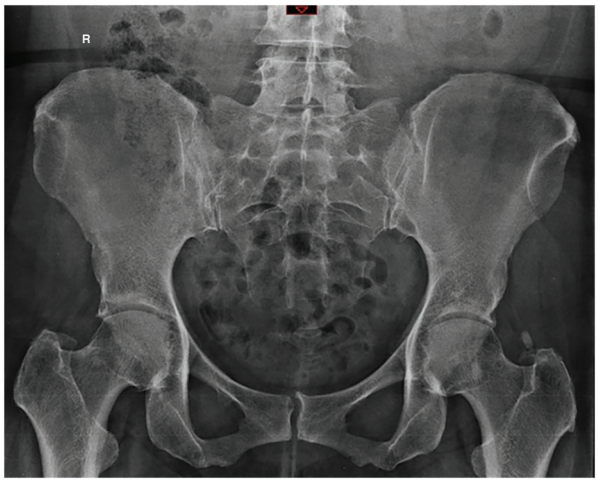


Figure 5. Power Doppler ultrasound images of lateral epicondylitis (long axis) in a female patient with radiographic axial spondyloarthritis (Case 4). (A) At baseline, there is an irregular structure and a hypoechoic focus in the fibres of the common extensor tendon associated with hypervascularization. (B) After 12 weeks of treatment with upadacitinib, showing improvement in the structural changes.

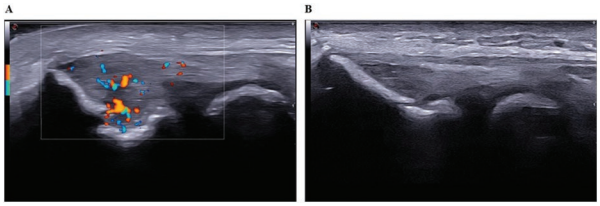
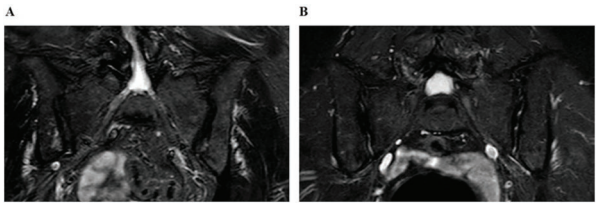


Figure 6. Magnetic resonance imaging of the sacroiliac joints using short tau inversion recovery in a female patient with radiographic axial spondyloarthritis (Case 4) (A) immediately before starting upadacitinib, showing bone marrow oedema and (B) after 1 year of upadacitinib showing resolution of oedema.



cardiovascular risk, we decided to start upadacitinib. We also speculated that a JAKi could have a positive effect on central sensitization and chronic pain and thereby help to improve the patient's arthromyalgias.

At the time of upadacitinib initiation, the patient had low back pain and elbow enthesitis, without peripheral joint involvement. CRP was 7.8 mg/L (normal range: 0–5), ESR was 34 mm/first hour (normal range: 0–25), the Health Assessment Questionnaire was 0.9, the ASDAS-CRP score was 7.8, and the BASDAI score was 7.5. MRI scan showed bone marrow oedema in T1-weighted and T2-weighted fat-suppressed images.

At the 3-month follow-up, the patient's spinal pain had resolved. Elbow ultrasound showed resolution of the epicondylitis (Figure 5). Even greater clinical improvement was noted after 6 months of upadacitinib, with further reduction in the ASDAS-CRP (from 7.8 to 6.2). In December 2022, the patient had SARS-CoV-2 infection, which was associated with a slight temporary worsening of low back pain. She took NSAIDs for 10 days and showed gradual symptom improvement. By week 52, the patient reported a 90% improvement in symptoms, CRP was 2.19 mg/L, ESR 13.0 mm/h, BASDAI score was 3.1 and ASDAI-CRP 1.7, indicating disease improvement and treatment effectiveness. After 2 years of upadacitinib therapy, the patient has maintained clinical, laboratory and imaging remission (Figure 6).

Conclusions

The case reports presented here demonstrate that upadacitinib has a rapid onset of action in patients with axSpA and can provide sustained clinical improvements, including LDA and remission, confirming the results of phase III clinical trials.[13,14] The cases and clinical trials demonstrate that upadacitinib is an effective therapeutic option in early disease as well as in patients who are biologic naive. The clinical efficacy and effectiveness of upadacitinib are likely related to its mechanism of action and ability to simultaneously inhibit several inflammatory pathways. The safety and tolerability profile of upadacitinib is similar to that of placebo, with a low rate of AEs of concern in patients with axSpA.

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