UPADACITINIB IN REAL CLINICAL PRACTICE: NEW HORIZONS IN THE TREATMENT OF AXIAL SPONDYLOARTHRITIS

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Abstract. Introduction: *Axial spondyloarthritis (axSpA) is an inflammatory disorder affecting the axial skeleton, accompanied by pain, restricted mobility, and other symptoms. The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a metric expressing disease activity, assessing inflammation and symptoms. In clinical trials, upadacitinib has demonstrated reduced axSpA activity, but real-world evidence remains limited.* ***Objective:*** *The objective of this study is to evaluate the therapeutic effectiveness of upadacitinib in axSpA by analysing its impact on symptoms, activity, and inflammatory markers in real clinical practice. Additional goals include comparing outcomes between biologic-naive and biologic-experienced patients, as well as assessing the influence of radiographic stage on upadacitinib's therapeutic response.* ***Methods:*** *Sixty-four patients with axSpA were enrolled in upadacitinib treatment. Among them, 42 were evaluated after 6 months and 13 after 12 months of therapy. ASDAS was assessed at various time points and analyzed based on prior experience with biologic drugs and radiographic stage of sacroiliitis.* ***Results:*** *A notable reduction in mean ASDAS values was observed after 6 months of Upadacitinib treatment (3.5 vs. 1.9, $p < 0.001$), with this reduction being sustained after 12 months (1.6 vs. 1.9, $p > 0.05$). A substantial proportion of patients (80.9%) achieved ASDAS values below 2.1 after 6 months, and this achievement was maintained after 12 months (84.6%, $p > 0.05$). No significant differences were found between biologic-naive and biologic-experienced patient subgroups (84.2% vs. 78.3%, $p > 0.05$). Similar trends were observed in the analysis of other parameters such as BASDAI, fatigue, pain, CRP, haemoglobin, and ESR. Upadacitinib increased the number of patients with low disease activity regardless of radiographic stage after 6 and 12 months (23.7 vs. 83.3% and 5.7 vs. 85.3%, $p < 0.001$).* ***Conclusion:*** *Upadacitinib proves to be effective in axSpA treatment. Regardless of demographic, clinical, and radiographic disease characteristics, as well as "biologic-naive/biofailure" status, Upadacitinib leads to ASDAS improvement after 6 and 12 months of treatment. This medication represents an effective tool in real-world clinical practice for controlling axSpA activity.*

Key words: *spondyloarthritis, upadacitinib, treatment, clinical practice*

Axial spondyloarthritis (axSpA) encompasses both radiographic and non-radiographic axSpA. It represents a chronic inflammatory disorder with a predilection for affecting the axial skeleton. Predominant symptoms commonly include chronic back pain and spinal stiffness, while peripheral and extra-musculoskeletal manifestations also frequently manifest [1]. Managing axSpA poses a challenge due to the complex nature of the diseases and the diversity of potential symptoms.

In recent years, novel biologic and targeted synthetic DMARDs have emerged as significant advancements in axSpA treatment, offering alternatives for patients who exhibit inadequate responses to standard therapies. Among these new treatments, upadacitinib, a Janus kinase (JAK) inhibitor, stands out. This medication has demonstrated its efficacy in various clinical trials for treating diverse forms of inflammatory joint disorders [2]. On the other hand, real-world clinical practice provides insights into patients' actual experiences with upadacitinib in everyday medical practice. It encompasses patients with various characteristics and circumstances, mirroring the authentic diversity of the patient population. In the real clinical context, various external factors can influence outcomes, making the data more representative of practical reality.

As of our current knowledge, there are no published real-world clinical practice data pertaining to

the assessment of the therapeutic effectiveness of Upadacitinib for spondyloarthritis indication.

Objective

The aim of the study is to assess the therapeutic effectiveness of upadacitinib in patients with spondyloarthritis by analysing its impact on symptomatology, disease activity, and inflammatory markers in real clinical practice conditions. Secondary objectives encompass comparing outcomes between patients with no prior experience of biological medications (bionaive) and those with previous unsuccessful experiences (biofailure), as well as evaluating the influence of radiological changes on the therapeutic response to upadacitinib.

Materials and methods

Patient Selection: The study included patients with axSpA, aged 18 and above, who initiated treatment with upadacitinib following a thorough clinical assessment, excluding other similar conditions, and in accordance with the current requirements of the NHIF (National Health Insurance Fund).

The diagnosis of axSpA is made based on the 2009 criteria [3]. Patients with axSpA who have structural changes on X-ray images of the sacroiliac joints, showing sacroiliitis, are classified as having radiographic axSpA (raxSpA), which is essentially the same as Ankylosing Spondylitis (AS) for all practical purposes. Those without such changes are classified as non-radiographic axSpA (nr-axSpA).

Study Design: The study is retrospective, encompassing data from the medical archive of the Rheumatology Clinic at UMHAT "Sv. Marina" – Varna. The data were collected during a specific period corresponding to the timeframe of upadacitinib application (from May 2022 to July 2023).

Measurements and Follow-up: Demographic indicators, initial and subsequent values of ASDAS, BASDAS, pain, fatigue, CRP, ESR, and haemoglobin, as well as the radiographic stages of sacroiliitis, have been analyzed for each patient. The values of ASDAS and BASDAI are calculated using widely recognized formulas. ASDAS and BASDAI are categorized according to accepted thresholds for disease activity – remission, low, moderate, and high activity – allowing for a detailed and objective assessment of upadacitinib's impact on axSpA activity. This helps determine whether the treatment contributes to improvement or if additional measures are necessary to control disease activity. The interpretation of results is facilitated, enabling adequate comparisons between different patient groups and different observation time points.

To examine the dynamics of fatigue and pain during Upadacitinib treatment, the first and second questions from the validated BASDAI scale were employed:

1. How would you describe the overall level of fatigue/tiredness you have experienced?
2. How would you describe the overall level of pain in your neck, back, or hip related to Ankylosing Spondylitis (AS) that you have experienced?

Values are collected using a Visual Analogue Scale (VAS), ranging from 0 to 10 for each question. To provide an objective assessment of upadacitinib's impact, average values for fatigue and back pain are used.

Erythrocyte Sedimentation Rate (ESR) in mm/h, C-reactive protein (CRP) in mg/l, and haemoglobin (Hb) in g/l were analyzed through standard laboratory tests with customary reference values before treatment initiation, after 6 and 12 months.

For the purposes of the study, conventional radiography of sacroiliac joints was analyzed for each patient, using a well-known classification in rheumatological practice for sacroiliitis staging.

Study Groups: Patients were categorized into two groups based on their experience with biological medications: those with no previous experience (bionaive) and those who had unsuccessful experiences (bioexperience). A comparative analysis was conducted both for the entire group at three time points – before treatment initiation, after 6 and after 12 months of upadacitinib therapy – as well as between the two groups at the same time points: at the beginning of treatment, after the sixth, and after the twelfth month. Throughout the entire period, all patients received a daily dose of 15 mg upadacitinib.

Statistical analysis was conducted using SPSS v23 for Windows. Descriptive statistics, chi-square test, and other non-parametric tests were employed for qualitative variables as necessary. For quantitative variables, mean values and standard deviations were calculated, and Student's t-test and analysis of variance were applied to determine the statistical significance of differences between groups and measurement time points. Correlation analysis and binomial logistic regression were utilized to analyse relationships and influences among different variables. The level of statistical significance was set at $p < 0.05$.

The results are presented using tabular and graphical methods.

The study was conducted in accordance with ethical standards outlined in the Declaration of Helsinki.

Results

The study included 64 patients with axSpA, divided into two groups – those without prior experience with biologic treatments (bionaive) and those with treatment failure from bDMARDs (biofailure). The groups were comparable in terms of age, gender, BMI, obesity status, duration of axSpA, and HLA-B27 positivity (Table 1). The mean age at diagnosis (44.8 vs. 40.4, p > 0.05) and the mean duration of axSpA before therapy initiation (6.5 vs. 7.4, p > 0.05) were similar between the two groups. HLA-B27 positivity was equally prevalent among bionaive and biofailure patients (66.7 vs. 85.7%, p > 0.05).

The subgroup named “Biofailure” includes patients who were primarily on previous therapy with TNFi (94.9%). Anti-IL17 therapy was only used in 5.1% of cases (p < 0.001). The average duration of bDMARDs use was 4.5 years before a secondary inadequate response was observed.

Significantly more patients in the “Bionaive” subgroup compared to the “Biofailure” subgroup have III and IV radiographic stages of sacroiliitis (96.0% vs. 74.4%). This difference is statistically significant (p = 0.026). Between 8.9% and 14.5% of the changes in radiographic sacroiliitis stage are attributed to previous experience with biological medications across the entire study group. Treatment with biological medications (TNFi) is identified as a protective factor for the likelihood of patients having III/IV radiographic sacroiliitis stage (OR 0.121, 95% CI 0.014-1.012, p = 0.051).

A significantly higher proportion of bionaive patients compared to biofailure patients had arterial hypertension (AH) (56.0% vs. 28.2%, p = 0.026).

Among the 62 axSpA patients, 42 completed a six-month treatment period, and 13 completed a twelve-month treatment period.

ASDAS-CRP

The mean value of ASDAS significantly decreased from 3.5 to 1.9 after 6 months of upadacitinib treatment (p < 0.001) and continued to decrease up to the 12th month (1.9 vs. 1.6, p = 0.02). Upadacitinib demonstrated comparable effectiveness both in biologic-naive and biofailure patients (Table 2). A significant proportion of patients successfully achieved an ASDAS value below 2.1 after the 6th month; these

Table 1. Clinical-Demographic Characteristics of Patients

	BIONAIVE	BIOFAILURE	P VALUE
Number (%)	25 (39.1)	39 (60.9)	NS
Age (yrs.) mean ± SD	52.7 ± 8.2	51.8 ± 12.0	NS
Gender Male (n, %)	14 (56.0)	24 (61.5)	NS
BMI kg/m^2 (mean ± SD)	26.8 ± 5.6	29.1 ± 6.0	NS
BMI > 30 kg/m^2	5 (20.0)	15 (38.7)	NS
Years at AS (mean ± SD)	44.8 ± 10.1	40.4 ± 12.1	NS
Duration of AS-yrs (mean ± SD)	9.6 ± 9.9	10.8 ± 12.5	NS
Duration of AS before treatment – years (mean ± SD)	6.5 ± 9.8	7.4 ± 12.3	NS
Duration of AS before bDMARDs – yrs (mean ± SD)	NA	6.6 ± 11.9	NA
Time of bDMARDs – yrs (mean ± SD)	NA	4.5 ± 3.6	NA
HLA B27 positive (n/N, %)	12/18 (66.7)	18 /23 (85.7)	NS
X ray stage sacroiliitis (n, %)			
nr-AxSpA	0	7 (17.9)	0.002
II	1 (4)	3 (7.7)	NS
III	12 (48.0)	9 (23.1)	0.040
IV	12 (48.0)	20 (51.3)	NS
AH (n, %)	14 (56)	11 (28.2)	0.026
Fatigue (Question 1)	6.5 ± 1.9	5.1 ± 2.6	0.025
Pain (Question 2)	8.0 ± 0.9	5.8 ± 2.1	< 0.001
BASDAI	6.5 ± 0.9	4.8 ± 2.1	< 0.001
ASDAS	3.7 ± 0.7	3.4 ± 1.2	NS

Abbreviations: Bionaive: Patients without prior experience with biologic medications. Biofailure: Patients with secondary non-responder status to biologic medications. SD: Standard Deviation. BMI: Body Mass Index.AS: Ankylosing Spondylitis. bDMARDs: Biologic Disease-Modifying Anti-Rheumatic Drugs. HLA: Human Leukocyte Antigen.nr-AxSpA: Non-radiographic Axial Spondyloarthritis. AH: Arterial Hypertension. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index. ASDAS: Ankylosing Spondylitis Disease Activity Score. NS: Non-significant, indicating that differences in the data obtained from the samples are not statistically significant.

results remained consistent up to the 12th month (80.9% vs. 84.6%, respectively, p > 0.05), with no significant difference observed between biologic-naive and biofailure patient subgroups (84.2% vs. 78.3%, respectively, p > 0.05) (Figure 1).

BASDAI

The mean value of BASDAI significantly decreased from 5.5 to 2.5 after 6 months of Upadacitinib treatment (p < 0.001) and remained at this level up to the 12th month (2.5 vs. 2.25, p > 0.05). A significant number of patients achieved a BASDAI value below 4 after the 6th month, and all patients reached this level by the 12th month (90.4% vs. 100%, respectively, p < 0.001), with no significant difference observed between biologic-naive and biofailure patient subgroups (94.7% vs. 95.4%, respectively, p > 0.05) (Table 2, Figure 2).

Fatigue

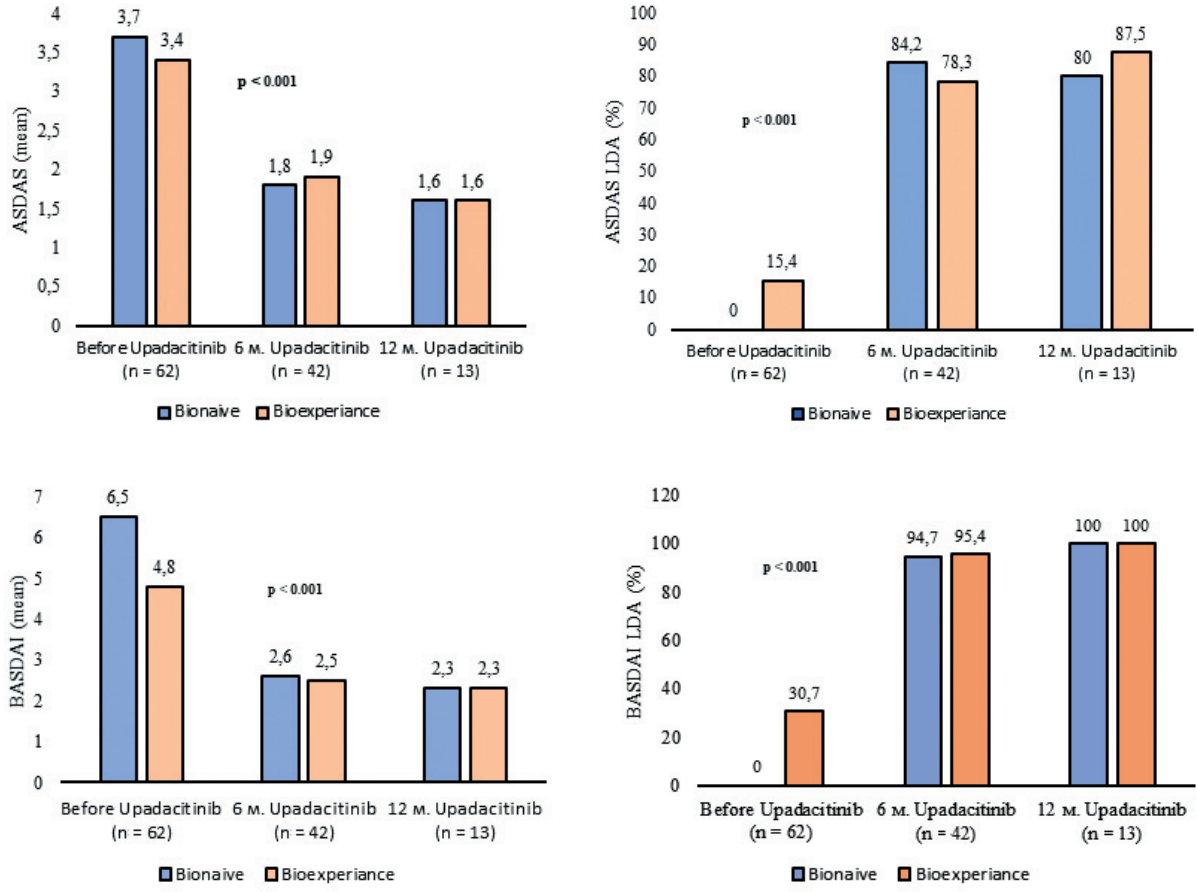
The mean level of fatigue decreased by more than two-fold after 6 months of upadacitinib treatment and remained at this level until the end of the study (5.6 vs. 2.5 vs. 2.5, p < 0.001, p > 0.05, respectively). Throughout the analyzed period, no statistically significant difference in the therapeutic response to upadacitinib was observed between the studied groups for this indicator (Table 2).

Pain

Treatment with upadacitinib led to a remarkable reduction in the intensity of pain, with this effect becoming evident after 6 months and continuing after 12 months (6.7 vs. 3.4 vs. 2.9; p < 0.001, p > 0.05, respectively). Notably, significantly more pain was reported by biologic-naive patients compared to biofailure patients after 12 months of treatment (3.6 vs. 2.5, p < 0.001).

Biological response

A remarkable reduction in CRP levels is observed after 6 months of treatment with Upadacitinib. The mean value decreases from 14.8 to 6.0 (p = 0.009). This effect is sustained after 12 months,



Abbreviations: Panel A – change in mean values; Panel B – change in the proportion of patients in LDA; ASDAS, Ankylosing Spondylitis Disease Activity Score, LDA – low disease activity, BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; X-ray stage of axSpa and therapeutic response to Upadacitinib

Fig. 1. Impact of Upadacitinib on AxSpA Activity (ASDAS, BASDAI) – Changes in Mean Values and Proportion of Patients with Low Disease Activity

Table 2. Indicators of axSpA activity in the studied groups during a one-year period of treatment with 15 mg/day. Upadacitinib

Analysis of therapeutic effectiveness	Before Upadacitinib (n = 64)			On the 6th month by Upadacitinib (n = 42)		p-value 0-6 m	At month 12 of Upadacitinib (n = 13)		p -value 6-12 m
	Bionaive n = 25	Biofailure (n = 39)	p-value	Bionaive (n = 19)	Biofailure (n = 23)	p -value	Bionaive (n = 5)	Biofailure (n = 8)	p-value
ASDAS -CRP (mean ± SD)	3.5 ± 1.0			1.9 ± 0.6		**< 0.001**	1.6 ± 1.2		0.02
	3.7 ± 0.7	3.4 ± 1.1	NS	1.8 ± 0.5	1.9 ± 0.5	NS	1.6 ± 0.2	1.6 ±0.2	NS
ASDAS-CRP < 2.1 (n, %)	6 (9.4)			34 (80.9)		< 0.001	11 (84.6)		NS
	0 (0)	6 (15.4)	0.04	16 (84.2)	18 (78.3)	0.72	4 (80.0)	7 (87.5)	NS
BASDAI (mean ± SD)	5.54 ± 1.8			2.58 ± 1.1		**< 0.001**	2.25 ± 0.6		NS
	6.5 ± 0.9	4.8±2.1	**< 0.001**	2.6 ± 0.7	2.5 ± 1.4	NS	2.3 ± 0.7	2.2 ± 0.6	NS
BASDAI < 4.0 (n, %)	12 (18.8)			38 (90.4)		< 0.001	13 (100)		< 0.001*
	0 (0.0)	12 (30.7)	0.002	18 (94.7)	22 (95.4)	NS	5 (100)	8 (100)	NS
Fatigue (mean ± SD)	5.6 ± 2.5			2.5 ± 1.3		< 0.001	2.5 ± 0.9		NS
	6.5 ± 1.8	5.1 ± 2.6	0.025	2.6 ± 1.4	2.3 ± 1.3	NS	2.4 ± 1.5	2.6 ± 0.5	NS
Pain (mean ± SD)	6.7 ± 2.1			3.4 ± 0.8		< 0.001	2.9 ± 0.9		NS
	8.0 ± 0.9	5.8 ± 2.1	< 0.001	3.6 ± 0.9	3.1 ± 0.7	NS	3.6 ± 0.8	2.5 ± 0.7	0.036
CRP - mg/L (mean ± SD)	14.8 ± 23.0			6.0 ± 14.1		0.009	2.8 ± 4.0		NS
	9.3 ± 14.2	14.9 ± 21.7	NS	4.0 ± 9.8	7.5 ± 16.5	NS	1.5 ± 2.4	3.0 ± 4.4	NS
Haemoglobin -g/L (mean ± SD)	137.4 ± 16.2			135.5 ± 12.9		NS	137.0 ± 11.2		NS
	139.8 ± 12.8	137.1 ± 17.4	NS	136.7 ± 11.7	134.2 ± 13.6	NS	142.6±11.6	131.6 ± 9.8	NS
ESR mm/h (mean ± SD)	30.6 ± 25.6			20.6 ± 20.9		0.011	15.1 ± 22.1		NS
	25.5 ± 22.6	35.2 ± 26.1	NS	14.1 ± 17.5	25.6 ± 21.7	NS	13.6 ± 15.5	15.8 ± 9.9	NS

Abbreviations: ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with CRP, BASDAI, Bath Ankylosing Spondylitis Disease Activity Index, CRP, C-reactive protein, ESR, erythrocyte sedimentation rate, p value 0-6, the comparison is between 6 months and before treatment, p -value 6-12 , the comparison is between 6 and 12 months of treatment

with the mean value further decreasing to 2.8 (p > 0.05). No significant differences in mean CRP values are observed based on previous experience with biological medications (Table 2).

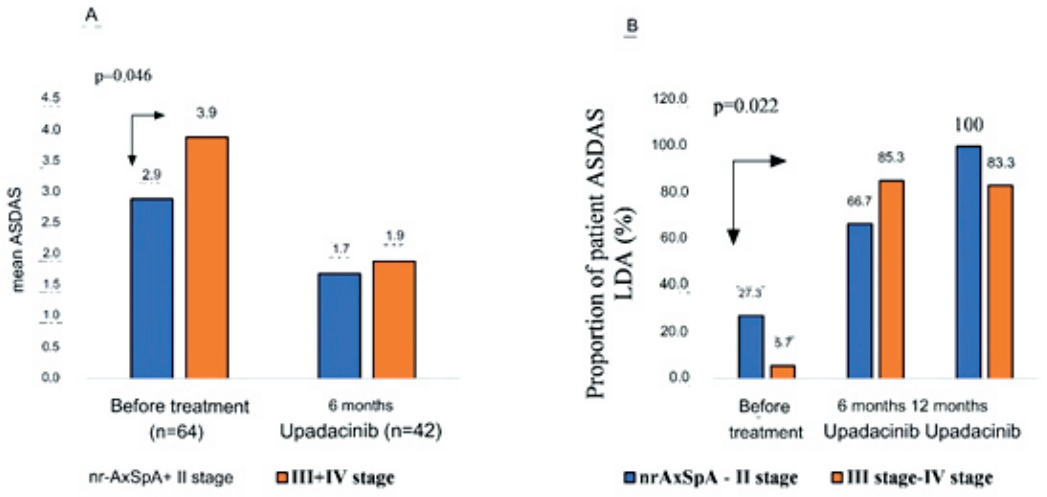
Similar effects are observed for ESR levels in patients with AxSpA treated with upadacitinib. A statistically significant reduction is recorded after 6 months of upadacitinib treatment (30.6 vs 20.6, p = 0.011), which is maintained after 12 months (20.6 vs 15.1, p > 0.05). No significant differences in mean ESR values are observed between the compared groups during treatment (Table 2).

The mean haemoglobin value before starting upadacitinib treatment is 137.4 g/L. After 6 months of upadacitinib application, the mean haemoglobin value decreases to 135.5 g/L, with the difference not being statistically significant. After 12 months, it is 137.0 g/L (p > 0.05). No significant difference in haemoglobin levels is observed during upadacitinib treatment based on bionaive/biofailure status (Table 2).

Before initiating therapy with upadacitinib, patients with non-radiographic/Stage II axSpA exhibit lower disease activity (measured by ASDAS) compared to patients with advanced structural changes in the disease (Stages III/IV axSpA) (ASDAS = 2.9 versus 3.6, p = 0.046). After 6 months of Upadacitinib therapy, the activity of axSpA significantly decreases in both subgroups, without observing a significant difference in ASDAS values between patients with non-radiographic/Stage II sacroiliitis and those with Stage III/IV sacroiliitis (1.7 versus 1.9, p > 0.05) (Figure 2, Panel A). Similar findings are observed at the 12-month mark of upadacitinib treatment.

It is observed that a significant portion of patients undergoing a 6-month treatment with upadacitinib achieve low disease activity (ASDAS < 2.1), and these results are consistent both in patients with non-radiographic and II stages of sacroiliitis, as well as those with III and IV radiographic stages of sacroiliitis (66.7% versus 85.3%, p > 0.05). These findings remain consistent throughout the entire study period (see Figure 2, Panel B).

During the study period, the following adverse reactions were reported with upadacitinib treatment: asymp-



Abbreviations: Panel A – mean values, Panel B – LDA; nr-AxSpA – non-radiographic axial spondyloarthritis, II, III, IV stage – x-ray stage sacroiliitis, ASDAS – Ankylosing Spondylitis Disease Activity Score, LDA – low disease activity.

Fig. 2. Change in ASDAS according to the radiographic stage of sacroiliitis during treatment with Upadacitinib

tomatic urinary tract infections (4.7%), allergic reactions (2.4%). In two patients (4.7%), lack of efficacy was observed as they continued to experience persistent pain symptoms, leading to discontinuation of treatment.

Discussion

The therapeutic strategy for Axial Spondyloarthritis (AxSpA) is of paramount importance in improving the quality of life for patients and reducing symptoms, including fatigue, pain, limited mobility, and inflammation [3]. The field of AxSpA treatment is rapidly evolving, encompassing diverse therapeutic approaches as well as novel medications [1].

One of the key treatment strategies for AxSpA involves the use of biologic (bDMARDs) and targeted synthetic drugs (tsDMARDs), which target specific molecules and pathways in the immune system [4]. The use of biologics and targeted synthetic drugs is based on results from clinical trials that highlight their effectiveness in reducing pain, inflammation, and improving functional ability.

Upadacitinib has been extensively studied in axial SpA through the broad clinical program SELECT AXIS 1, 2, PsA [5, 6, 7].

When discussing the therapeutic strategy, it is important to consider an individualized approach for each patient. This approach involves assessing disease severity, sacroiliitis radiographic stage, comorbidities, and cardiovascular risk factors. Furthermore, the decision to choose a specific therapy should be based on current national and international recommendations that are updated based on new scientific discoveries.

In recent years, aside from TNF and IL-17 inhibitors, JAK inhibitors are also being considered as potential treatment options for AxSpA [8]. At present, recommendations include the use of JAKi in treatment, but due to the lack of direct comparative studies, establishing their efficacy priority over other AxSpA treatments is challenging. Current practice usually involves initiating treatment with TNFi or IL-17i, though recent recommendations do not exclude the possibility of selecting JAKi as an initial option [9].

The results from real-world clinical practice, presented by us in a cohort of 62 patients with AxSpA, reveal that within routine clinical practice, rheumatologists engaged in systemic treatment have significantly older patients compared to those in clinical trials [10].

Upadacitinib is considered for the treatment of axSpA in our real-world clinical setting relatively late after the diagnosis, with similar delays observed in bionaive patients and those with previous bDMARDs treatment failure. Similar findings are reported by other authors who observe that there is a period of 5 to 7 years between the onset of symptoms and the diagnosis of axSpA, and treatment initiation occurs even later [11].

In the bioexperience subgroup, the average duration of treatment with biologic agents before signs of an unsatisfactory response become apparent and established is 4.5 years. This represents a significant difference between the subgroups. Within this subgroup, there is an essential period of successful condition management through biologic therapy, after which secondary treatment failure develops [12].

Only after this average 4.5-year period of bDMARDs application are JAKi introduced.

Out of all patients included in the study, 60.5% exhibit bioexperience and are suitable for upadacitinib treatment. For patients without prior experience with biologic agents, upadacitinib is used as a first-line DMARD.

Patients included in the Upadacitinib treatment predominantly exhibit advanced structural changes (82.8% have III/IV radiographic stages of sacroiliitis). Among patients with non-radiographic or II radiographic stages of axSpA, those with prior experience in biologic therapy are mainly present (90.9%). Although not our primary objective, it can be assumed that these observations are linked to the prolonged application of bDMARDs before secondary non-responder status develops. Similar results have already been published by other authors [13, 14, 15]. The patients with non-radiographic/II radiographic stage axSpA are significantly fewer compared to the total number of patients, which limits us from drawing definitive conclusions about the relationship between biologic treatment and radiographic changes. It is important to emphasize that patients without prior treatment experience ("Bionaive") are more likely to have a more advanced stage of radiographic changes.

Delving deeper into the data, we can observe an intriguing aspect related to the presence of co-existing arterial hypertension (AH) in the two distinct patient subgroups. According to the data, over half of the patients without prior experience with biologic agents show signs of AH, which is nearly twice as much compared to those who have had prior experience with biologics. The inference that can be drawn is that the administration of the primary preceding biologic medication (TNFi) might be associated with a lower likelihood of AH. Such an association has already been identified, and there are available findings indicating reduced cardiovascular risks in TNFi treatments [16, 17].

Upadacitinib demonstrates remarkable therapeutic effectiveness, reflected in ASDAS, BASDAI scores, levels of fatigue and pain, reductions in ESR and CRP values, both in patients without prior experience with biologic drugs and those with secondary non-response to biologics. Our scientific findings from this study regarding the therapeutic effectiveness of upadacitinib in patients with axSpA in real-world clinical practice correspond to the respective data derived from the SELECT AXIS clinical program. The proportion of patients achieving disease inactivity or low disease activity in axSpA when treated with 15 mg Upadacitinib for 6 and 12 months (according to ASDAS) align with the results reported in clinical trials of this medication. Within the framework of the SELECT AXIS clinical program, 65% of patients treated with upadacitinib achieve ASDAS < 2.1, which is entirely consistent with our reported results [18].

The results obtained from the 6 and 12-month treatment with Upadacitinib do not correlate with the previous treatment of patients with axSpA (bionaive/bioexperience) (16 out of 19, 84.2% versus 18 out of 23, 78.3%, $p > 0.05$, respectively), suggesting that upadacitinib is equally effective both in patients without prior treatment and in those with secondary failure to bDMARDs.

Similar trends are seen in the fully subjective composite measure BASDAI. The average change in BASDAI after 6 months of 15 mg upadacitinib therapy is over 50% of the initial value and is sustained until the end of the study. The relative proportion of patients with BASDAI < 4 is 90.4%, an impressive result. Meanwhile, this outcome is better than the known data from SELECT AXIS 1 [17]. A possible explanation for this difference might be that over half of the patients in the present study have prior experience with biologic drugs. Their initial average BASDAI score is significantly lower compared to biologic-naive patients (4.8 vs. 6.5, $p < 0.001$, mean difference 1.68, 95% CI 0.7-2.62). These patients exhibit better initial results at the start of the study, which might contribute to the better therapeutic response after Upadacitinib application. The degree of fatigue and intensity of spinal pain, included as questions 1 and 2 in the BASDAI and ASDAS assessments, respectively, demonstrate a similar dynamic throughout the analyzed period.

Upadacitinib shows successful and comparable results both in patients with non-radiographic SpA and those with more advanced radiographic sacroiliitis scores. These observations align with the data from upadacitinib's clinical program for the SpA indication. It has been proven to demonstrate effectiveness in cases of both radiographic and non-radiographic SpA [18].

In conclusion, the results of our study highlight the significant therapeutic effectiveness of upadacitinib in patients with axial spondyloarthritis (axSpA) under real clinical conditions. Upadacitinib's ability to reduce disease activity, measured by ASDAS and BASDAI, as well as its positive impact on pain, fatigue, and inflammatory biomarkers, emphasizes its crucial role in improving patients' quality of life.

The results also demonstrate that upadacitinib shows successful results both in patients who are

naïve (biologic naïve) and those who have previously failed other biologics (biofailure). This aspect underscores the flexibility and potential of upadacitinib to be individually assessed when selecting a treatment regimen for different patient subgroups.

In alignment with data from clinical programs and based on our results, it can be concluded that upadacitinib is a valuable tool in managing axial spondyloarthritis. This medication contributes to a significant improvement in disease activity, regardless of prior experience, and presents itself as a significant contribution to best care for patients with this chronic and debilitating condition.

Библиография / References

3. Navarro-Compán V, Sepriano A, El-Zorkany B, Heijde D van der. Axial spondyloarthritis. Annals of the Rheumatic Diseases 2021; 80:15.
4. Braun J, Kiltz U, Baraliakos X. Management of Axial Spondyloarthritis – Insights into Upadacitinib. Drug Des Devel Ther. 2022 Oct 19;16:3609-3620.
5. Rudwaleit M, Van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selectionAnnals of the Rheumatic Diseases 2009;68:777-783.
6. Magrey MN, Danve AS, Ermann J, Walsh JA. Recognizing Axial Spondyloarthritis: A Guide for Primary Care. Mayo Clinic Proceedings 2020;95:2499-2508.
7. Zhao SS, Harrison SR, Chan A et al. Treatment of axial spondyloarthritis with biologic and targeted synthetic DMARDs: British Society for Rheumatology guideline scope. Rheumatology Advances in Practice 2023;7.
8. Heijde D van der, Song I-H, Pangan AL 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 2019;394:2108-2117.
9. Deodhar A, Van den Bosch F, Poddubnyy D et al. Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 2022;400:369-379.
10. Baraliakos X, Ranza R, Östör A et al. Efficacy and safety of upadacitinib in patients with active psoriatic arthritis and axial involvement: results from two phase 3 studies. Arthritis Research & Therapy 2023;25.
11. Paroli M, Caccavale R, Paroli MP et al. Janus Kinase Inhibitors: A New Tool for the Treatment of Axial Spondyloarthritis. Int J Mol Sci. 2023;24(2):1027.
12. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 updateAnnals of the Rheumatic Diseases 2023;82:19-34.
13. Jones A, Harrison N, Jones T et al. Time to diagnosis of axial spondylarthritis in clinical practice: signs of improving awareness? Rheumatology (Oxford). 2014;53(11):2126-2127.
14. Juanola X, Ramos MJM, Belzunegui JM et al. Treatment Failure in Axial Spondyloarthritis: Insights for a Standardized Definition. Adv Ther. 2022;39(4):1490-1501.
15. Dougados M, Maksymowych WP, Landewé RBM, et al. Evaluation of the change in structural radiographic sacroiliac joint damage after 2 years of etanercept therapy (EMBARK trial) in comparison to a contemporary control cohort (DESIR cohort) in recent onset axial spondyloarthritis. Ann Rheum Dis 2018;77:221-7.
16. Molnar C, Scherer A, Baraliakos X. Rheumatologists of the Swiss clinical quality management program. TNF blockers inhibit spinal radiographic progression in ankylosing spondylitis by reducing disease activity: results from the Swiss clinical quality management cohort. Ann Rheum Dis 2018;77:63-9.
17. Micheroli R, Kissling S, Bürki K, et al. Sacroiliac joint radiographic progression in axial spondyloarthritis is retarded by the therapeutic use of TNF inhibitors: 12-year data from the SCQM registry. RMD Open 2022;8:e002551.
18. Nair S, Singh Kahlon S, Sikandar R et al. Tumor Necrosis Factor-Alpha Inhibitors and Cardiovascular Risk in Rheumatoid Arthritis: A Systematic Review. Cureus. 2022;14(6):e26430.
19. Mehaffey E, Majid DSA. Tumor necrosis factor-α, kidney function, and hypertension. Am J Physiol Renal Physiol. 2017;313(4):F1005-F1008.
20. Van der Heijde D, Song I-H, Pangan AL et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, 2019.
21. Deodhar A, Van den Bosch F, Poddubnyy D et al. Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2022 Jul 30;400(10349):369-379.

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