Research Paper

Sulfasalazine's Impact on Ankylosing Spondylitis: A Retrospective Analysis

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Non-steroidal anti-inflammatory drugs and biologic therapy are recognized as standard treatments for ankylosing spondylitis. However, in developing countries like Turkey, the cost of biological treatments can escalate to significant levels. Our study aims to assess the effectiveness of sulfasalazine in axial symptoms, typically considered a secondary treatment in ankylosing spondylitis. We conducted a retrospective analysis of the medical records of patients diagnosed with ankylosing spondylitis. These patients were prescribed sulfasalazine due to the persistence of axial symptoms. After a 3 mo course of sulfasalazine treatment, patients were assessed for changes in sediment and C-reactive protein values, ankylosing spondylitis disease activity score-sedimentation rate and ankylosing spondylitis disease activity score-C-reactive protein values, visual analog scale, bath ankylosing spondylitis disease activity index, and bath ankylosing spondylitis functional index results and morning stiffness durations. In this study, conducted with sulfasalazine treatment, significant improvements were observed across multiple parameters. Morning stiffness duration decreased in 22 patients. Median C-reactive protein levels decreased from 9.99 mg/l (range: 2-53, interquartile range: 12.21) to 6.81 mg/l (range: 1-18, interquartile range: 8.16). Similarly, the median ESR reduced from 20.53 mm/h (range: 4-48, interquartile range: 15.47) to 12.81 mm/h (range: 2-33, interquartile range: 10.57). Ankylosing spondylitis disease activity score-C-reactive protein scores improved from 3.62±0.732 to 2.67±0.93, and ankylosing spondylitis disease activity score-ESR scores improved from 3.54±0.66 to 2.57±0.80. Moreover, patients reported lower visual analogue scale scores, decreasing from 7.39±1.44 to 5.58±1.97. The global disease evaluation by doctors showed a decrease from an average score of 6.33±1.47 (range: 4-10) to 5.11±1.68 (range: 2-8). Ankylosing spondylitis quality of life questionnaire scores improved from 7.92±2.41 to 5.36±2.73. Bath ankylosing spondylitis disease activity index scores decreased from 6.31±1.70 to 4.37±1.76, and bath ankylosing spondylitis functional index scores improved from 3.76±1.98 to 2.79±1.63. These improvements were statistically significant across all measured parameters before and after sulfasalazine treatment ($p<0.05$). In developing countries like ours, where access to biological drugs which derived from living organisms, can be challenging for economically disadvantaged individuals with limited socioeconomic resources, and where the probability of inducing side effects such as infections, an elevated risk of cancer, and neurological diseases is a concern, sulfasalazine could be considered a more affordable and relatively safer option before resorting to biological treatments for managing ankylosing spondylitis.

Key words: Sulfasalazine, ankylosis, spondylitis, spondyloarthritis, adalimumab

Ankylosing Spondylitis (AS) is a chronic inflammatory multi-systemic disease that can manifest with various symptoms in the clinic. The condition is characterized primarily by axial skeletal involvement[1]. The primary clinical feature of the disease is persistent inflammatory low back pain, which can arise from sacroiliitis and spondylitis. Inflammation and ankylosis typically develop throughout the clinical progression. The affected areas in AS are specifically identified as the cartilage-bone junctions and entheses[2,3]. AS is recognized

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as the most common and prototypical member of a group of diseases known as Spondyloarthropathy (SPA). This group also encompasses conditions such as reactive arthritis, inflammatory bowel disease-associated spondyloarthritis, psoriatic SPA, and undifferentiated types[4]. From an epidemiological perspective, the overall prevalence of SPA in Caucasians is approximately 1.5 %-2 %, with AS prevalence at around 0.5 % in Turkey. While AS was historically considered a male-oriented disease it is now acknowledged as more homogeneous.

The male/female ratio is approximately 2.5. Studies have demonstrated that radiological damage and progression tend to be more severe in men. Additionally, treatment compliance is lower in men, with higher Bath AS Disease Activity Index (BASDAI) and AS Quality of Life (ASQOL) questionnaire scores observed in women[5]. Patients with AS may experience profound fatigue, persistent back and waist pain that doesn't subside with rest but improves with exercise, stiffness, and pain and swelling in various areas such as knees, hips, and ribs. Some patients may develop abnormal new bone formation in vertebral corners or bone protrusions in enthesial areas. The cumulative impact of pain, structural damage, and extraspinal symptoms contributes to functional impairment and disability. Individuals with AS are twice as likely to experience vertebral fragility fractures compared to the general population. This heightened risk may lead to serious conditions, including atlantoaxial subluxation and cauda equina[6]. The primary treatment objectives in AS are to alleviate pain, reduce stiffness, and preserve axial spine movements. To achieve these goals, non-pharmacological methods such as regular exercise and lifestyle changes may be recommended for patients[7].

In recent years, the concept of disease modification has gained increasing significance. This term encompasses not only improving symptoms but also altering the natural clinical course of the disease[8]. Considering the disease mechanism as a focal point, it can be asserted that treatments aiming to modify the disease intend to both reduce inflammation and limit new bone formation. Presently, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are recognized as a standard treatment for AS. According to the EULAR/ASAS (European Association of Rheumatism-Assessment in Spondyloarthritis International Society), biological agents (anti-Tumor Necrosis Factor (TNF) therapy) are the preferred choice for treating axial SPA. They are recommended as the subsequent line of treatment[9]. However, in developing countries, the cost of biological treatments, meaning those made from a living organism or its products, such as genetically engineered proteins, can escalate to significant levels such as governments face significant challenges in covering the expenses of these treatments within their healthcare budgets. Moreover, anti-TNF treatments (such as etanercept, adalimumab, golimumab and infliksimab) may induce side effects in patients, including serious infections, tuberculosis, an elevated risk of cancer, and neurological diseases. Meanwhile, there exists a debate regarding the effectiveness of sulfasalazine, actively employed in treating peripheral joint involvement in AS, in addressing axial symptoms[10].

Our study aims to retrospectively assess the effectiveness of sulfasalazine, typically considered a secondary treatment in AS, over a specific time frame in patients diagnosed with AS whom we are monitoring in the outpatient clinic. We hypothesize that sulfasalazine, despite being a secondary treatment, demonstrates significant therapeutic benefits in managing axial symptoms, potentially offering a viable alternative for patients who face challenges accessing biological treatments.

MATERIALS AND METHODS

We conducted a cross-sectional, descriptive, retrospective analysis of the medical records of patients diagnosed with AS. Our study was approved by the local ethics committee on 30th January 2024 with the research protocol (No: 2024.10.01.10). The study included patients over the age of 18 who had either sacroiliitis features on imaging with at least one additional SPA feature or HLA-B27 positivity with at least two other SPA features. These patients visited the rheumatology outpatient clinic between 1st July, 2023 and 1st January, 2024 and had previously used NSAIDs, either as single or multiple doses, for varying durations. Pregnant and lactating women, patients allergic to sulfa drugs, patient's already taking sulfasalazine, and those who required biologic drugs were excluded from the study. There were no comorbidities in patients that could influence disease assessment and treatment response. These patients were prescribed sulfasalazine one gram twice daily due to the persistence of axial symptoms like low back pain, and morning stiffness. The examination encompassed demographic characteristics, age

at disease onset, disease duration, comorbidities, medications used for comorbidities, NSAIDs used for pain and their duration, duration of morning stiffness, sedimentation rate, C-Reactive Protein (CRP), AS Disease Activity Score-CRP (ASDAS-CRP), ASDAS-sediment (ASDAS-sedim) values, Visual Analogue Scale (VAS) pain values, patient self-assessed global disease assessments, physician-assessed global disease scores, ASQOL, BASDAI, Bath AS Functional Index (BASFI) values. All data were retrieved from the hospital data system and patient files. After a 3 mo course of sulfasalazine treatment, patients diagnosed with AS were assessed for changes in sediment and CRP values, ASDAS-sedim and ASDAS-CRP values, VAS, BASDAI, and BASFI results, patient-assessed global disease status, physician-assessed global disease indices, and morning stiffness durations. Demographic data of the AS patients in this study were documented. ASAS20 responses of the patients were calculated, and the achievement of ASAS20 response before and after treatment was evaluated. To assess disease activity before and after sulfasalazine treatment, we statistically compared the quality of life questionnaires and AS disease activity or functional indices which mentioned.

Statistical analysis:

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 27.0 statistical package program. Variables of the patient group participating in the study are presented as mean and standard deviation. For the comparisons of patient variables and after sulfasalazine variables, the paired sample t-test was used for normally distributed variables, and the Wilcoxon test was used for non-normally distributed variables. A $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

In this study, which involved 36 patients diagnosed with AS attending the rheumatology outpatient clinic during the specified periods, eleven (31 %) of the patients were female, and 25 (69 %) were male. The average age of all patients in our study was 37.47 y (22 to 53). The demographic details of the study population can be seen in Table 1. When sulfasalazine was prescribed, 34 of our patients (94.4 %) reported experiencing low back pain. Among those before sulfasalazine, three individuals (8.3 %) reported a significant reduction in low back pain 3 mo after initiating the drug. Examining morning stiffness, we observed varying durations, with the longest being 4 h and the shortest being 30 min. Comparing morning stiffness before and after sulfasalazine, we noted a reduction in the duration for 22 patients (61 %), and morning stiffness completely disappeared in six patients (16.6 %). When assessing patients for laboratory parameters, median CRP level before sulfasalazine treatment was 9.99 (2-53, Interquartile Range (IQR): 12.21) mg/l. After 3 mo of drug use, we observed a decrease in median CRP level to 6.81 (1-18, IQR: 8.16) mg/l. CRP values decreased in 24 patients (66 %).

The median sediment value before sulfasalazine treatment was 20.53 (range: 4-48, IQR: 15.474) mm/h, and we observed a decrease to a median of 12.81 (range: 2-33, IQR: 10.57) mm/h. In total, we noted a reduction in sediment values in 29 patients (80 %). The average ASDAS-CRP was 3.62±0.732 before treatment, and it decreased to 2.67±0.93. In terms of ASDAS-ESR values, the mean level was 3.54±0.66, and it decreased to 2.57±0.80. We observed a decrease in ASDAS-CRP values in 30 patients (83 %) and a decrease in ASDAS-ESR values in 31 patients (86 %). When assessing our patients using the patient's assessed VAS for pain and fatigue, we observed that the average VAS score was 7.39±1.44. After treatment, the average decreased to 5.58±1.97. A decrease in VAS score was observed in 27 of our patients (75 %). In terms of the global evaluation of the disease from the doctor's perspective, the average score was 6.33±1.47 (4-10), which decreased to 5.11±1.68 (2-8). The average ASQOL score was 7.92±2.41, which decreased to 5.36±2.73. The quality of life survey scores decreased in 28 patients (77.7 %) after sulfasalazine use. We assessed BASDAI, finding an average score of 6.31±1.70 before sulfasalazine treatment, which decreased to 4.37±1.76. The average BASFI score was 3.76±1.98 before treatment and it decreased to 2.79±1.63.

The BASDAI score decreased in 31 patients (86 %) and functional index score decreased in 27 patients (75 %). These improvements were statistically significant across all measured parameters before and after sulfasalazine treatment ($p<0.05$) (Table 2). When evaluating our patients based on the ASAS20 response rate, we found that 47.2 % of our patients achieved ASAS20 responses after 3 mo of sulfasalazine use. SPA encompasses a group of chronic inflammatory rheumatic diseases, categorized into

forms primarily affecting axial or peripheral joints. AS stands out among those predominantly affecting the axial form. Traditionally, the male/female ratio in AS, particularly in ancient times, was defined as 10/1.

However, recent literature suggests a shift in this ratio, now stated as 3/1[11]. Toward the end of 2016, this ratio decreased even further and was reported as 1.03/1 in Swiss publications, indicating a notable shift in the gender distribution of AS[12]. In our study, we determined the male/female ratio to be 2.22, a result consistent with the literature. The age of onset has long been regarded as a crucial factor in defining chronic low back pain, particularly in individuals at a high risk of axial SPA. Studies investigating patients with axial SPA worldwide have consistently reported the occurrence of low back pain before the age of 45[13]. ASAS classification criteria also state that the age of onset of low back pain is before 45[14]. In our study, consistent with the literature, the maximum age of onset of low back pain was found to be 44 y. Sulfasalazine belongs to the class of Disease-Modifying Antirheumatic Drugs (DMARDs). It functions as a prodrug, undergoing conversion to its active metabolites through bacterial action in the large intestine. The active metabolites include sulfapyridine and 5-aminosalicylic acid, which inhibit B cell function but not T cell function, suppress the production of antibodies, and inhibit the secretion of inflammatory cytokines[15]. Sulfasalazine has demonstrated efficacy in addressing peripheral joint involvement in AS and other rheumatic diseases. However, its impact on axial involvement remains a topic of controversy in the literature. The ASAS 2010 update explicitly mentioned the use of traditional DMARDs for peripheral joint involvement but noted insufficient evidence supporting their use in axial involvement. The update indicated that a marginal positive effect of sulfasalazine with a rather limited effect size in AS cannot be excluded. However, no strong recommendation was made to support its use. Instead, rheumatologists were advised to consider a trial of sulfasalazine for a limited period, typically not exceeding 4 mo, after which further benefit is unlikely. Additionally, it was noted that the majority of studies suggest some efficacy of sulfasalazine in patients with peripheral SPA and in the prevention of anterior uveitis[16].

TABLE 1: DESCRIPTIVE STATISTICS OF DEMOGRAPHIC DETAILS

	Mean±SD (min-max)
Age (years)	35.61±8.92 (22-53) y
BMI (kg/m^2)	24.81±3.76 (17.3-32.65)
Onset of back pain (years)	29.25±6.00 (20-44) y
Age of disease (years)	5.974±5.96 (3 mo-25 y)

TABLE 2: STATISTICAL RELATIONSHIP OF LABORATORY VALUES BEFORE AND AFTER THE USE OF SULFASALAZINE

	Before sulfasalazine	After sulfasalazine	p
Doctor global assessment	6.33±1.47 (4-10)	5.11±1.68 (2-8)	<0.0001
Morning stiffness (min)	89.17±53.41 (30-240)	42.64±30.60 (0-120)	<0.0001
Sedimentation (mm/h)	20.53 (4-48)	12.81 (2-33)	<0.0001
CRP (mg/l)	9.99 (2-53)	6.81 (1-18)	<0.003
BASDAI	6.31±1.70 (2.2-9.6)	4.37±1.76 (1.1-7.5)	<0.0001
BASFI	3.76±1.98 (1-8.8)	2.79±1.63 (1-6.3)	<0.0001
ASQoL	7.92±2.41 (4-12)	5.36±2.73 (0-11)	<0.0001
ASDAS-CRP	3.62±0.732 (0.2-4.8)	2.67±0.93 (0.1-4.6)	<0.0001
ASDAS-sedim	3.54±0.66 (0.3-5.4)	2.57±0.80 (0.2-4.6)	<0.0001
VAS global	7.39±1.44 (5-10)	5.58±1.97 (3.5-8.6)	<0.0001

Firstly, a 2020 study conducted in South Korea explored the impact of traditional DMARDs on the radiological progression of AS. In this study involving 1280 participants, it was reported that sulfasalazine showed no significant effect on radiological progression. However, it was noted that the study lacked control over patient's regular medication use. Additionally, the influence of sulfasalazine or other DMARDs on other inflammatory markers remains unclear in the study[17]. Conversely, a 2020 single-center prospective study conducted in India involving 232 axial SPA patients investigated the responses to sulfasalazine and traditional DMARD combinations based on ASAS20 criteria. The study revealed that this response was achieved in approximately 55 % of patients[18]. In our study, aimed at contributing to the ongoing debate in the literature, we observed a noteworthy reduction in morning stiffness durations, and other activity indexes. A significant number of our patients showed a decrease in inflammation markers. However, a study conducted by Braun *et al*.[19] reported no decrease in ESH and CRP values with the use of sulfasalazine. Conversely, other studies we encountered in the literature noted a decrease in inflammatory markers in 67.7 % of patients with the use of sulfasalazine[20,21]. In line with these studies, we found a statistically significant relationship in terms of sedimentation rate and CRP levels. In an observational study conducted in China, 320 AS patients were examined. A comparison between patients using NSAIDs alone and those using sulfasalazine in addition to NSAIDs revealed greater reductions in disease activity and ASDAS-CRP scores in 59.8 % of the patients who added DMARDs[22]. In a 2012 study conducted in our country, patients were divided into two groups. Sulfasalazine was added to one group, while a traditional DMARD was added to the other group in addition to sulfasalazine. The results of the study showed a 20 % decrease in the need to switch to biological treatment[23]. In the study conducted by Khanna *et al*.[20], a 61 % decrease in the BASDAI score was observed, and a significant proportion of our patients experienced reductions in both BASDAI and BASFI scores (86 % and 75 %, respectively). Moreover, in line with the study conducted by Ganapati *et al*.[18] in India, almost half of our patients achieved the ASAS20 response. The enhancements in quality of life parameters and disease activity with sulfasalazine seen in our study may be linked to the reduction in the need for NSAIDs. Braun *et al*.[19] also reported a decrease in the need for NSAIDs with 3 mo sulfasalazine treatment[19]. This can be interpreted as an effect in protecting against side effects of NSAIDs. Additionally, a recent study conducted in India at the end of 2023 evaluated the effectiveness and safety of sulfasalazine in 33 AS patients.

In this study, BASDAI scores decreased in 40.08 %, and BASFI scores decreased in 48.6 % of patients. The study concluded that sulfasalazine could be a safe alternative, similar to the results of our study[24]. To conclude, in developing countries like ours, where access to biological drugs may be limited due to financial challenges, sulfasalazine emerges as a viable alternative to these more costly treatments, provided that careful monitoring for potential adverse effects such as blood dyscrasias, pancreatitis, interstitial nephritis, hepatitis, and hepatic failure is undertaken[15]. Given its relatively lower cost and potential positive impact, sulfasalazine could provide significant value in resource-constrained settings by offering a more affordable option for managing AS. To better understand its efficacy and optimize treatment strategies, future research in rheumatology should focus on conducting multicenter and large-scale studies. Such studies would help to comprehensively evaluate the effectiveness of sulfasalazine and its impact on patient outcomes in developing countries. Furthermore, for AS patients who do not respond to NSAIDs or traditional DMARDs, it would be prudent to explore and develop more cost-effective biologic drugs, thereby expanding treatment options and improving accessibility for all patients. Our study has several limitations, including the small number of patients and our single-center evaluation, which may constrain the generalization of findings. The limited sample size reduces the statistical power of our results, making it more challenging to detect significant differences or trends that might exist in a larger cohort.

Additionally, being a single-center study means that the findings may be influenced by specific local practices, patient demographics, and other site-specific factors, which may not be representative of other settings. To address these limitations, future research should focus on conducting prospective studies that involve a larger population. Expanding the sample size would improve the robustness of the data and increase the reliability of the conclusions drawn. Furthermore, conducting multicenter studies would allow for the inclusion of diverse patient populations

and varied clinical practices, thereby enhancing the external validity and generalizability of the findings. Comparative studies are also necessary to validate our results. Specifically, research comparing sulfasalazine with other first-line treatments for the condition under investigation would provide a more comprehensive understanding of its efficacy and safety profile. Such studies could identify potential advantages or disadvantages of sulfasalazine relative to alternative treatments, thereby guiding clinical decision-making and optimizing patient care.

Conflict of interests:

The authors declared no conflict of interests.

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