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Research Article

Age-Related Variations in Treatment Patterns for Axial Spondyloarthritis

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Abstract

Aim: This study examines treatment patterns and preferences among patients diagnosed with Axial Spondyloarthritis (AxSpA) across different age groups.
Material and Method: Ankara Bilkent City Hospital registry enabled a comprehensive cross-sectional analysis of 2,811 patients stratified into three age groups: 18-40, 41-55, and over 55 years. These groups were compared in terms of their treatments.
Results: Our findings indicate an increasing prevalence of female patients and comorbidities with age. Medication usage patterns showed a trend towards increased use of Methotrexate and Colchicine with age, while Sulfasalazine and Leflunomide were more commonly prescribed in older age groups. Notably, the use of biologic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs), including anti-Tumor Necrosis Factor (anti-TNF)", "anti-Interleukin (anti-IL) agents, demonstrated a declining trend with advancing age, though not reaching statistical significance. This trend was also reflected in gender-specific treatment distributions, where no significant difference was found in bDMARDs administration among patients over 55 years, contrasting with a higher usage rate in younger male patients.
Conclusion: Our study highlights a shift towards more conservative treatment approaches, such as increased conventional synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) use in older patients, likely due to their safety profile and the specific challenges associated with treating older adults, including higher comorbidity rates and medication side effects. These findings emphasize the need for personalized treatment strategies and suggest potential adjustments in clinical practices to better accommodate the aging population, advocating for ongoing research to optimize treatment efficacy and safety for elderly patients with AxSpA.

Keywords: Axial spondyloarthritis, elderly, antiTNF, antirheumatic agents

INTRODUCTION

Axial spondyloarthropathy (AxSpA) is an inflammatory rheumatic disease that primarily affects the spine and peripheral joints. Characterized by chronic low back pain that typically begins before the age of 45, AxSpA may also manifest extra-articular symptoms such as uveitis, inflammatory bowel disease, and psoriasis (1). In 2009, AxSpA was categorized into ankylosing spondylitis (AS) and non-radiographic AxSpA (nr AxSpA). AS is identified through radiographic evidence of sacroiliitis, whereas nr AxSpA is diagnosed when such changes are not sufficiently apparent. Over time, the term AS has evolved into radiographic AxSpA in clinical parlance (2).

The disease's incidence ranges dramatically—from 0.4 per 100,000 in Iceland to 15 per 100,000 in Canada, as revealed by systematic reviews. In patients with nr-AxSpa, the data are incomplete because they are insufficient. In terms of prevalence, figures vary from 9 to 30 per 10,000, influenced by the demographic and ethnic makeup of the study population (3). A study in Türkiye reported an AS prevalence of 540 per 100,000 (4).

Gender disparities in AxSpA have traditionally posited a higher prevalence in males, especially within the AS cohort. However, no significant gender disparity is observed in nr-AxSpA patients. While axial symptoms predominate in males, peripheral joint and extra-articular manifestations appear equally across genders. The age of diagnosis is comparable between genders, albeit diagnostic delays are more prevalent among women (5,6).

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The management of AS focuses on alleviating symptoms, preserving functionality, preventing complications such as contractures from spinal involvement, addressing extra-articular manifestations, and supporting the patient's psychosocial well-being. A holistic approach that combines pharmacological and non-pharmacological treatments is essential. This regimen may include lifestyle changes, patient education, and regular physical or physiotherapy exercises. Treatment typically begins with non-steroidal anti-inflammatory drugs (NSAIDs), which are effective in 50-70% of cases (7,8). For patients who do not respond to NSAIDs, options like conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or biological agents are considered, tailored to the patient's pattern of involvement, extraarticular findings and comorbidities. Although csDMARDs are crucial in managing rheumatoid arthritis, their efficacy in AxSpA, particularly for spinal symptoms, is not well-supported by evidence. However, they may be beneficial for peripheral symptoms, with studies indicating that sulfasalazine (SSZ) is more effective than methotrexate in treating peripheral arthritis (9,10). Meanwhile, biological agents are increasingly utilized based on current guidelines, with studies suggesting they maintain efficacy without significant serious side effects that would necessitate discontinuation of treatment (11).

The treatment efficacy and tolerability of NSAIDs in elderly AxSpA patients mirror those in younger cohorts, although there is a noted decrease in tolerability. The research on biological drugs in older patients is limited due to their frequent exclusion from randomized controlled trials. Nonetheless, preliminary studies suggest that these agents can be safely administered in elderly populations. The limited amount of research evaluating the impact of treatments on comorbidities and potential side effects in elderly patients highlights a substantial knowledge gap in the management of AxSpA among this demographic. Although the evidence remains sparse, recent studies support the safe administration of biological drugs in the treatment of elderly AxSpA patients, suggesting a cautious optimism for their use in this age group. This emerging data underscores the necessity for more comprehensive studies to better understand the efficacy and safety of these treatments in older populations, particularly in the context of their broader health challenges (11).

This study aims to analyze treatment preferences and patterns across different age groups, enhancing our understanding of AxSpA's clinical management across diverse patient demographics. This will provide insights into the clinical management of AxSpA in different patient populations.

MATERIAL AND METHOD

The Ankara Bilkent City Hospital registry, established in 2023, serves as a pivotal resource for the retrospective analysis and documentation of patients diagnosed with inflammatory rheumatological conditions. By June 2023, a longitudinal aspect was incorporated, transforming the registry into a single-center, observational, longitudinal cohort. This computerized system, characterized by its duplication-disabled feature, meticulously records data based on patients' medication reports, pertaining to various inflammatory rheumatological diseases monitored in our clinic.

The focus of the current study is on patients diagnosed with AxSpA was determined by rheumatologists' clinical evaluations. Eligibility for inclusion in the study was restricted to individuals aged 18 and above. Utilizing a cross-sectional approach, we analyzed retrospective cohort data from 2811 AxSpA patients who had complete and relevant records up between 2019 and 2023. Exclusion criteria for the study included individuals under the age of 18. Patients who did not have complete and relevant medical records for the period between 2019 and 2023 were also excluded.

Key variables examined in this study included demographic data, comorbidities, and treatment regimens. Patients were categorized into three age groups: Group 1: 18-40, Group 2: 41-55, and Group 3: over 55 years. Within these age strata, we assessed the choice of treatment modalities. The analysis focused on the usage of (ever/never) csDMARDs, Anti-TNF agents (such as etanercept,adalimumab, infliximab, certolizumab pegol and golimumab), and Anti interleukin treatments (including secukinumab, ustekinumab, ixekizumab and guselkumab). The Ethics Committee of Ankara Bilkent City Hospital approved the study protocol (Date=17.08.2022, Ethical approval number=E1-22-2826).

Statistical Analysis

Statistical analyses were conducted using Jamovi (v2.3.22, Sydney, Australia). Both visual methods (such as histograms and probability plots) and analytical methods (like the Kolmogorov-Smirnov test) were employed to assess the normality of the variables. Continuous variables that followed a normal distribution were presented as mean ± standard deviation (SD). Categorical variables were expressed as numbers and percentages. Comparisons between groups were performed using ANOVA for continuous variables and the chi-square test for categorical variables

RESULTS

2811 AxSpa patients were evaluated retrospectively. The mean age of patients in the first group was 32.8 (5.2), while 47.5 (4.2) in the second group, and 62.6 (6) at the third group. Percentage of female patients were found to be higher with increased age (39.1%, 45.8% vs 54.6%, $p<0.001$). As expected, having comorbidities increased with age (29%, 59% vs 81.6%, $p<0.001$, respectively).

Table 1 delineates the comparative usage of medications across the age-stratified groups (18-40 vs 41-55 vs over 55, until 2023). Significant differences are observed in the use of specific medications between the age groups. There were trends in methotrexate (5.2%, 6.5 %, and 7.9%,

p=0.115) and colchicine (7.8%, 9.3%, vs 11%, p=0.1) use being more frequent in patients over 55 years of age. Sulfasalazine (35.2% in Group 1, 40.1% in Group 2, and 42.1% in Group 3, p=0.01) and leflunomide (0.4%,0.6% vs 1.7%, p=0.008) were markedly more used in patients over 55 years of age. Corticosteroid use was comparable between the groups.

Tablo 1. Drug choices in axial spondyloarthritis patients according to age

	Age 18-40 (N=1030)	Age 41-55 (N=1263)	Age>55 (N=518)	Total (N=2811)	p value
Age, Mean (SD)	32.8 (5.2)	47.5 (4.2)	62.6 (6.0)	44.9 (11.8)	<0.001[1]
Sex, Female n(%)	403 (39.1%)	578 (45.8%)	283 (54.6%)	1264 (45.0%)	<0.001[2]
Comorbidity, n(%)	298 (29.0%)	744 (59.0%)	422 (81.6%)	1464 (52.2%)	<0.001[2]
Methotrexate, n (%)	54 (5.2%)	82 (6.5%)	41 (7.9%)	177 (6.3%)	0.115[2]
Leflunomide, n (%)	4 (0.4%)	7 (0.6%)	9 (1.7%)	20 (0.7%)	0.008[2]
Sulfasalazine, n (%)	363 (35.2%)	507 (40.1%)	218 (42.1%)	1088 (38.7%)	0.012[2]
Colchicine, n (%)	80 (7.8%)	117 (9.3%)	57 (11.0%)	254 (9.0%)	0.103[2]
Corticosteroids, n (%)	31 (3.0%)	34 (2.7%)	20 (3.9%)	85 (3.0%)	0.425[2]
AntiTNF, n (%)	469 (45.5%)	578 (45.8%)	207 (40.0%)	1254 (44.6%)	0.062[2]
AntiIL, n (%)	46 (4.5%)	50 (4.0%)	17 (3.3%)	113 (4.0%)	0.529[2]

1: Linear Model ANOVA, 2: Pearson's Chi-squared test

In terms of biologic drug usage, a trend towards decline with age in the use of anti-TNF agents (45.5% in Group 1, 45.8% in Group 2, and 40% in Group 3, p=0.06) and IL inhibitors were noted (4.5% in Group 1, 4.0% in Group 2, and 3.3% in Group 3, p=0.53). However, these are not statistically significant.

When patients over 55 years of age receiving antiTNF were compared in terms of gender, no statistically significant difference was found between both genders. 40.4% of male patients over 55 years of age were receiving antiTNF treatment, while 39.6% of female patients were receiving antiTNF treatment (p=0.844) . However, when the general group was analyzed, it was seen that 51.1% of male patients received antiTNF while 36.7% of female patients received antiTNF (p<0.001). In the light of this information, it can be said that antiTNF treatment is increased in elderly female patients.

DISCUSSION

The therapeutic landscape for patients diagnosed with AxSpA is witnessing an incremental expansion, broadening the scope of potential treatments available. Despite these advancements, managing older patient demographics, especially those with concurrent comorbidities, presents a significant challenge. This demographic is notably under-represented in randomized controlled trials (RCTs), a cornerstone for establishing evidence-based practices. Consequently, this under-representation precipitates a palpable dearth of high-level evidence, critical for guiding treatment selection in older patients. We aimed to investigate the impact of this lack of evidence on treatment selection with real-life data. Our observations revealed a trend towards increased use of methotrexate and colchicine with advancing age, whereas sulfasalazine and leflunomide were more commonly used at older ages. The administration of bDMARDs (anti-TNF and anti-IL) showed a declining trend with age, albeit not reaching statistical significance. However, while more male patients received biologic treatment in the general patient group, there was no significant difference between the genders in patients over 55 years of age receiving bDMARDs.

A pivotal finding of this study is the age-related increase in csDMARD usage and a corresponding decrease in bDMARD administration. Reviewing the literature reveals mixed evidence regarding the efficacy of conventional csDMARDs on axial symptoms in AS, with several studies indicating limited impact on disease activity indices such as BASDAI and BASMI. However, some research suggests benefits of csDMARDs on various assessment scales, though these findings are not universally significant (12,13). A Cochrane review on sulfasalazine found no significant impact on pain, disease activity, or radiographic progression, with only one study noting minor clinical improvements (14). Leflunomide was not found to be effective in patients with axial findings (15). However, there are also publications in the literature suggesting that csDMARDs are effective. In a double-blind randomised controlled trial involving 67 patients, significant changes in ASDAS, BASDAI and BASMI were seen in the sulfasalazine group compared with placebo (16). Similarly, in the study by Dougados et al, improvements in functional indexes were observed with sulfasalazine and it was shown to reduce the need for NSAID use (17).

For peripheral involvement, csDMARDs may be the first choice. There is a view that sulfasalazine in particular is effective in peripheral joint involvement. In the literature,

csDMARDs have been shown to be more effective in studies of ankylosing spondylitis, where the patient groups are predominantly composed of patients with peripheral arthritis. Nissila et al. showed that the use of sulfasalazine up to 3 g per day in a patient group dominated by peripheral arthritis led to improvements in acute phase reactants, morning stiffness and chest expansion (18). In another group of 99 patients with AS dominated by peripheral arthritis, improvement in clinical parameters (morning stiffness, ESR, number of painful and swollen joints) was observed (19).

Although the place of csDMARDs in the treatment of rheumatoid arthritis is well known, there are not enough studies to support the use of csDMARDs in AS. The increase in the rate of use with age can be interpreted as a preference for csDMARDs over bDMARDs due to safety concerns of physicians. The increased risk of developing potential drug-related side effects and the fact that patients have more comorbidities are behind these safety concerns. In addition to safety concerns, the fact that peripheral involvement is more common in older patients (late-onset AXSPA) may be another reason (20). There are studies in the literature on treatment management in elderly patients in RA, where there is a higher proportion of elderly patients, but there is also more limited data in AS patients. In a review evaluating treatment management in elderly AS patients, NSAIDs, which are known to have an effect on stiffness and pain in AS, may not be used in elderly patients due to an increased risk of side effects. Sulfasalazine has not been studied in elderly patients with AS, but may be preferred in RA patients, although GIS intolerance increases with experience. Close monitoring of liver enzymes, creatinine and haemogram is recommended with methotrexate (21).

There are studies in the literature on the use of biologics in older patients. Although no significant difference was found in terms of efficacy, there are different opinions that side effects are different in elderly patients. In patients with rheumatoid arthritis, which is known to have a higher proportion of elderly patients, no difference in biological treatment was found with advanced age (22). In another study, etanercept was found to be safer in older patients, but medically important infections were more common in patients aged >65 years (23). In a study of 83 RA and AS patients aged >70 years treated with infliximab, the risk of serious infection was found to be 6.5 times higher than in younger patients. It was observed that the risk of tuberculosis in RA patients receiving infliximab was not higher in the older group (24). This information may explain the hesitation to use biologic therapies in older patients in routine follow-up.

An intriguing aspect of our research highlights a disparity in the utilization of biological therapies between genders within the general patient cohort, with a higher usage rate observed in males. However, this trend equalizes within the elderly patient group, where the employment of biological therapies does not significantly differ between sexes. Traditionally, AxSpa has been more commonly associated with the male gender, yet no significant gender difference is noted in nr AxSpA patients. Despite a higher prevalence of axial manifestations in males, the occurrence of peripheral joint and extra-articular symptoms appears comparably across genders. Furthermore, the age at initial diagnosis remains consistent between sexes, although research indicates a more frequent occurrence of delayed diagnoses in females, a factor potentially contributing to increased disease activity in older female patients. (5,6,25). In our study, the proportion of female patients increased with increasing age. There are also publications in the literature supporting that BASDAI and quality of life scores are higher in female patients. This may explain why the need for biological treatment in women tends to increase with age, and why the rate of biological treatment in women in the older age group is similar to that of men, in contrast to the younger group.

Our investigation is subject to several noteworthy constraints. Firstly, the data utilized in this study were obtained through a retrospective review of patient records. Despite the implementation of an electronic patient record system that mandates all treatments to be logged, the risk of incomplete data capture persists. Additionally, the study's reliance on data sourced exclusively from one center constrains the applicability of its findings to broader populations. Furthermore, the lack of data on disease activity, axial or peripheral predominance means that cause and effect cannot be fully established in some conclusions, and such conclusions have been avoided.

CONCLUSION

In summary, our investigation illuminates the nuanced differences in treatment strategies for AxSpA across various age demographics. While csDMARDs are not typically endorsed by clinical guidelines for the treatment of NSAID-resistant patients, their inclusion in practical treatment plans suggests a deviation towards personalized care. This adjustment is particularly pronounced in the management of older patients, highlighting the complexities and necessitating bespoke treatment modifications. Our findings indicate an age-related increase in the preference for csDMARDs and a corresponding decline in the propensity towards biologics, suggesting that while guideline-based treatment algorithms provide a foundation, the ultimate therapeutic decision is influenced by the unique characteristics of each patient. Continued clinical research is essential to develop effective treatments to meet the health needs of the ageing population and improve the quality of life of older people.

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