DOI: https://doi.org/10.54393/pjhs.v5i06.1376

PAKISTAN JOURNAL OF HEALTH SCIENCES
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 6 (June 2024)

Original Article

Disease Patterns of Ankylosing Spondylitis Associated Treatment Patterns and Drug Utilization among Affected Patients

Muhammad Umer Rashid[1], Amina Khurshid[1], Hassan Shaukat[1], Fahd Farooq Ashraf[1], Muhammad Haseeb Lodhi[1], Amir Naveed[2] and Muhammad Farrukh Habib[3*]

[1]Department of General Medicine, Pakistan Emirates Military Hospital, Rawalpindi, Pakistan
[2]Department of Forensic Medicine, Amna Inayat Medical College, Sheikhupura, Pakistan
[3]Department of Management Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan

ARTICLE INFO

Keywords:
Ankylosing Spondylitis, Autoimmune Disease, Axial Skeleton, Disease Patterns

How to Cite:
Rashid, M. U., Khurshid, A., Shaukat, H., Ashraf, F. F., Lodhi, M. H., Naveed, A., & Habib, M. F. (2024). Disease Patterns of Ankylosing Spondylitis Associated Treatment Patterns and Drug Utilization among Affected Patients: Disease Patterns of Ankylosing Spondylitis . Pakistan Journal of Health Sciences, 5(06). https://doi.org/10.54393/pjhs.v5i06.1376

***Corresponding Author:**
Muhammad Farrukh Habib
Department of Management Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan
muhammadfarrukhhabib@gmail.com

Received Date: 28th March, 2024
Acceptance Date: 28th June, 2024
Published Date: 30th June, 2024

ABSTRACT

Ankylosing Spondylitis is disease with significant morbidity. With biological DMARDs, treatment is revolutionized compared to conventional options. The article will discuss disease pattern, risk factors and treatment response of various drugs on this disease. **Objective:** To evaluate the prevalence, risk factors, treatment patterns, and drug utilization associated with Ankylosing Spondylitis (AS) among patients in clinical practice. **Methods:** This prospective cross-sectional study was done at territory care hospital in Rawalpindi from June 23 to December 23. Data comprised of methods to identify AS, particular tests used to verify diagnosis, numerical and clinical traits of patients included. Study also peruse percentage of patients identified as HLA-B27 positive, Time elapsed between initial symptom appearance and clinical diagnosis of AS, satisfaction of classification criteria and treatment strategies employed, such as advanced therapies for controlling AS disease activity. **Results:** Mean values for current disease occurrences and functional index outcomes were 3.3 ± 2.1 and 1.8 ± 1.09 in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were used, respectively. Patients in study received treatment with adalimumab (43%) and Infliximab (27%) for an average period of 3.1 ± 2.1 years. Treatment satisfaction showed convenience domain had lowest score (4.2), whereas scores for side effects, effectiveness, and global satisfaction were 93.7, 75.41, and 73.81, respectively. **Conclusions:** Among bDMARDS adalimumab was most administered followed by Infliximab. Better therapeutics have improved patient satisfaction. Research revealed a significant decrease in productivity as a result of AS.

INTRODUCTION

Ankylosing Spondylitis (AS) is one of the chronic autoimmune disease primarily affecting the axial skeleton, leading to prolonged and debilitating illness [1]. It is characterized by the presence of fomenting and gruesome back pain, which ultimately results in structural and functional impediment and a less in overall standard of life. Males exhibit a higher prevalence rate compared to females, with a mean ratio of 3.4 to 1 [2]. Around 80% of individuals experience the initial symptoms of AS before reaching the age of 30, whereas less than 5% of people manifest symptoms after the age of 45 [3]. Due to the compromised physiological functioning experienced by individuals diagnosed with AS, the disease exerts a substantial impact on occupational circumstances. Individuals diagnosed with AS exhibit impairments in various occupational domains, including uninterrupted work performance, prolonged standing, ambulation, sustained focus, interpersonal interactions and productivity in terms of both quantity and quality, as well as adherence to deadlines. The aforementioned constraints lead to a reduction of production by 6.3% as compared to individuals in good health or alternatively, an increase in working hours by 7.1% [4]. Given the absence of a cure for AS, the primary objective of treatment approaches

DOI: https://doi.org/10.54393/pjhs.v5i06.1376

revolves around managing symptoms, mitigating joint deterioration, and attaining or sustaining disease remission [5]. Commonly used therapeutic options include non-steroidal anti-inflammatory drugs (NSAIDs), Disease-Modifying Antirheumatic Drugs (DMARDs), and newer biological DMARDs. NSAIDs are often recommended as the initial treatment to manage pain and stiffness [4]. In cases where NSAIDs prove to be ineffective, the use of bDMARDs is advocated [6]. This recommendation is supported by significant evidence indicating a prompt and lasting response, particularly in younger patients with a brief duration of the disease, elevated levels of inflammatory indicators, and favorable functional grade [7]. Several biologics, such as adalimumab, secukinumab, infliximab, and ixekizumab, have received approval for the management of AS in patients who have not shown a satisfactory response to NSAIDs. The diagnosis and management of AS involve the involvement of many specialists, such as rheumatologists and orthopedists, who may adopt distinct therapeutic approaches [1].

This study aimed to investigate the frequency, risk factors of Ankylosing Spondylitis (AS) its corresponding treatment strategies and medication usage among those affected patients within the context of clinical practice.

METHODS

After the ethical approval from institutional review board, via Letter ID A/28/ER/17/23, this prospective cross-sectional study was conducted at Territory Care Hospital Rawalpindi from June 2023 to December 2023. Through non-probability consecutive sampling, 200 participants above age 19 years, presenting the symptoms of AS of either gender were incorporated in the present study. Sample size was calculated using WHO calculator, Confidence interval was 95% and margin of error was 5%. The prevalence of Ankylosing Spondylitis (AS) was 0.32% [8]. Patients less than 19 years of age, have any other connective tissue co-morbidity were excluded from the present study. The collected data encompassed various aspects related to the diagnosis of Ankylosing Spondylitis (AS) by physicians. This encompassed their methodology for diagnosing AS, the particular tests and evaluations used to validate the diagnosis and The study examined the statistical and patient related characteristics. It also analyzed the proportion of patients who tested positive for HLA-B27 and the duration linking initial clinical signs and Ankylosing Spondylitis diagnosis, the satisfaction of classification criteria and the treatment strategies employed, such as advanced therapies for controlling disease activity in Ankylosing Spondylitis. The study also evaluated the onus of disease reported by patients with AS, using validated criteria. Participants were asked to voluntarily take part in doing various standard evaluations to determine disease progression, general wellbeing status, the study assessed the Quality of Life (QoL) and productivity of participants. It analyzed the demographic and clinical characteristics of the study patients, as well as their treatment approaches. Descriptive statistics were used to present treatment satisfaction (TSQM) and productivity loss, including percentages for definite data and mean with standard deviation for numerical data. The data of the study was analyzed in SPSS version 20.0.

RESULTS

Table 1 presented the demographic characteristics of the 200 study participants recruited for the study. Mean age of the participants was 52.34 ± 12.32 years, with 67% were males, the average BMI was 25.2 ± 3.5 kg/m^2, mean time span of disease was 6.4 ± 3.2 years. About 51% of the participants have secondary school education, and 79% were breadwinning.

Table 1: Demographic Parameters of the Study Participants (N=200)

Variables	N (%)/(Mean ± SD)
Age (Years)	52.34 ± 12.32
Male	134 (67%)
Females	66 (33)
Education (Secondary School or Less)	102 (51%)
Education (College or More)	98 (49%)
Employment Status (Employed)	157 (79)
Employment Status (Unemployed)	43 (22)
BMI (Kg/m^2)	25.2 ± 3.5
Duration of Disease (Years)	6.4 ± 3.2
Comorbidity (Yes)	58 (29%)
BASFI	1.8 ± 1.09
BASDAI	3.3 ± 2.1
Injection Pain, VAS	2 ± 2.12

In table 2, the mean values for current disease progress and functional index scores were reported as 3.3 ± 2.1 and 1.8 ± 1.09 in the Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), respectively. The individuals in the study had received treatment with any Tumour Necrosis Factor Inhibitor (TNFi) for an average period of 3.1 ± 2.1 years. At the time of study enrolment, adalimumab (43%) and Infliximab (27%) were the most frequently utilized TNFi among the four evaluated in this investigation. The current TNFi were administered for an average duration of 5.0 ± 1.3 years of adalimumab and 5.3 ± 2.4 years for etanercept. A significant number of patients (37%) had been maintained on a low dose, defined as below the permitted dose, in the year preceding their enrolment in the study. In comparison to the other TNFi, adalimumab was administered at a lower dosage in the majority of patients. Approximately 49% of the participants with TNFi were given a pen-type device being spoken for subcutaneous injection, as shown in table 2. In relation to concurrent therapies, 26% of the patients utilized conventional disease-modifying antirheumatic medications (cDMARDs), 72% employed NSAIDs, and 26%

DOI: https://doi.org/10.54393/pjhs.v5i06.1376

utilized steroids. In the examination of treatment satisfaction, it was observed that the convenience domain had the lowest score (4.2), whereas the scores for side effects, effectiveness, and global satisfaction were 93.7, 75.41, and 73.81, respectively.

Table 2: Disease Pattern of the Study Participants (N=200)

Disease Pattern	N=200 N (%)/(Mean ± SD)
TNFi Therapy From Initiation (Years)	3.1 ± 2.1
Current TNFi Treatments	
Infliximab	54 (27%)
Etanercept	40 (20%)
Adalimumab	85 (43%)
Golimumab	20 (10%)
Duration of Current TNFi Medication in Years	
Infliximab	4.3 ± 2.1
Etanercept	5.3 ± 2.4
Adalimumab	5.0 ± 1.3
Golimumab	3.2 ± 1.9
Doses of the Current TNFi Therapy Administered in the Past Year Per Admission	
Approved	127 (63%)
Low	73 (37%)
Infliximab	
>6 mg	20 (37%)
<6 mg	34 (63%)
Adalimumab	
<40 mg	60 (71%)
>40 mg	25 (29%)
Etanercept	
<50 mg	25 (63%)
>50 mg	15(37%)
Golimumab	
<50 mg	2 (10%)
>50 mg	18 (90%)
BASDAI Score Categorized by Treatment and Dosage	
Approved	3.2 ± 2.3
Stunted	3.4 ± 1.7
Infliximab	
>6 mg	3.3 ± 1.8
<6 mg	2.9 ± 1.5
Etanercept	
>40 mg	3 ± 1.9
>40 mg	3.7 ± 2.1
Golimumab	
<50 mg	3.1 ± 1.2
>50 mg	2.8 ± 1.4
BASDAI Score Categorized by Treatment and Dosage	
Approved	1.6 ± 1.2
Stunted	1.5 ± 1.9
Infliximab	
>6 mg	2 ± 2.2
<6 mg	1.3 ± 1.9
Adalimumab	
>40 mg	1.7 ± 1.8
>40 mg	1.5 ± 1.6
Etanercept	
<50 mg	2.3 ± 1.8
>50 mg	2.5 ± 1.2
Golimumab	
<50 mg	2.1 ± 1.2
>50 mg	1.3 ± 1.3
Approach of Device Type Bespoken	
Subcutaneous Syringe	54 (27%)
Intravenous	48 (24%)
Subcutaneous Pen	98 (49%)
Accompanying Use Of DMARD (Yes)	39 (20%)
Concomitant Use Of NSAID (Yes)	143 (72%)
Auxiliary Use Of Steroids (Yes)	52 (26%)

Table 3 represented the productivity loss of the study participants with AS. The loss of productive hours being more than total absence from duty. Partial absence from job is also slightly higher than total absence. Productivity loss from disease has also significant financial burden as shown in the table 3.

Table 3: Productivity Loss of Patients with AS (N = 200)

Productivity Loss of Patients	Mean ± SD
Days exerted if not sick with as during the last four weeks	24.5 ± 6.2
Number of full days absent from work in the last 4 weeks	1.2 ± 2.3
Partial absences on work days in the last 4 weeks (days); half-day absence	1.32 ± 2.6
Self-assessed job recital in the last 4 weeks	6.5 ± 1.5
Productive hours lost due to absenteeism In the last 4 weeks	5.9 ± 24.3
Productive time lost owing to reduced work Performance in the last 4 weeks (hours)	54.3 ± 32.2
Hours of lost productivity	55 ± 34.2
Yearly expense due to employee absenteeism In Pakistani rupees	449242 ± 65430
Yearly expenses due to presenteeism yearly Expenses due to lost productivity (pkr)	3368711 ± 45760
Yearly expenses due to lost productivity (pkr)	3817953 ± 132987

DISCUSSION

Ankylosing spondylitis (AS) is a chronic, inflammatory and debilitating disease mainly affecting the axial spine and manifest with myriad of clinical signs and symptoms. The hallmark features include chronic back pain and progressive spinal stiffness. AS is characterized by the involvement of the spine and sacroiliac (SI) joints and peripheral joints, digits, and entheses. Involvement of sacroiliac joint radiologically confirms the diagnosis of ankylosing spondylitis. AS effects any gender but it effects males more than females due to HLA-27 and complex genetic interaction between various genes. approximately 2:1 ratio [9]. In 2009–2010, the National Health and Nutrition Examination Survey estimated that the prevalence of axial

DOI: https://doi.org/10.54393/pjhs.v5i06.1376

AS among adults in the USA varies from 0.9 to 1.4%.[10] The number of AS cases in Europe and Asia is estimated to be 1.30–1.56 million and 4.63–4.98 million, respectively.[11] The onset of AS usually occurs before the age of 45 years[12] ,when adults are in their peak productive years, and patients experience limited physical function, significant loss of work productivity, and a decreased quality of life during this period after disease onset [13]. Thus AS is an important healthcare and socioeconomic issue. Various risk factors have been identified in pathogenesis of ankylosing spondylitis, recently role of gut microbiota is one of them and an area of extensive research. [14] A metagenomics study analyzed gut microbial DNA from 211 Chinese individuals and found that patients with AS had an increased load of *Prevotella melaninogenica, Prevotella copri*, and *Prevotella* sp. C561, and decreases in *Bacteroides* sp [15]. Furthermore, role of Klebsiella pneumoniae has also been implicated in pathogenesis of AS [16]. Cigarette smoking aswell as E-smoking has also been indentified as risk factor in progression of AS [17]. Patients in Pakistan with Ankylosing Spondylitis (AS) who underwent TNFi medication were the subjects of this prospective cross-sectional study, which sought to analyse treatment satisfaction, treatment pattern, and productivity loss. In addition, we investigated the related aspects that help us comprehend the entire disease burden that AS patients face and how TNFi might be practically applied to their treatment. The primary objective of treatment for AS is to mitigate symptoms, enhance and sustain spine flexibility and proper posture, minimize functional impairments, preserve occupational capacity, and mitigate the potential consequences associated with the condition [18]. The effectiveness of TNFi in treating AS has been extensively documented, and their utilization has become an integral part of clinical protocols [19]. Internationally, there exists variation in the utilization of TNFi medications across different countries, as no specific TNFi treatment is universally endorsed over its counterparts. The findings of this study indicate that adalimumab was the most commonly utilized TNFi among the four available options in Pakistan, with Infliximab being the subsequent choice in terms of usage frequency. Sweden and Brazil exhibit a somewhat similar pattern to Pakistan in terms of the frequency of prescribing adalimumab, but etanercept is more typically given in the United States and Canada [20, 21]. In the present investigation, it was observed that around 37% of the participants had been consistently prescribed a low dosage of their current TNFi for a duration of one year prior to their enrolment in the study. The disease activity exhibited by individuals receiving low-dose TNFi treatment were found to be comparable to those observed in patients receiving the recommended dosage of TNFi. Amid the TNFi assessed in this study, adalimumab, specifically, exhibited a longer duration of maintenance and was administered at a lower dosage for a greater percentage of patients. The observed inclination towards an extended duration of adalimumab utilization in the present investigation does not aligns with the findings of a prior study conducted in Korea, which demonstrated a prolonged persistence with etanercept as a second-line treatment option for TNFi [22]. This investigation noted the simultaneous use of a tumour necrosis factor inhibitor with traditional disease-modifying antirheumatic medications (cDMARDs) for the treatment of AS, despite the lack of data about the efficacy and safety of cDMARDs in this setting. The European League Against Rheumatism (EULAR) guidelines for the control of AS from 2016 suggest that patients with peripheral arthritis may benefit from this combination medication [23]. The study found that patient satisfaction with TNFi was much greater than to treatment gratification reported for other unabating diseases in Pakistan. It was observed that the convenience domain had the lowest score (4.2), whereas the scores for side effects, effectiveness, and global satisfaction were 93.7, 75.41, and 73.81, respectively. Based on the analysis of TSQM data obtained from prior research, it was observed that individuals diagnosed with postmenopausal osteoarthritis indicated their level of satisfaction with treatment in the dominion of effectiveness, adverse effects, expedience, and worldwide contentment as 56, 64, 63, and 54, respectively. Patients with irregular heart rate who received vitamin K treatment manifested their satisfaction scores as 58, and 56 in the corresponding TSQM domains. In this study, the domain of treatment convenience exhibited the lowest reported satisfaction among the four domains. In the present investigation, it was observed that individuals participating in the research work experienced a mean absence duration of 1.2 full days and 1.3 partial days throughout the preceding four-week period. The observations of this research was similar with those of a prior findings based on Korean employees, which documented an average of 5.22 hours of work absenteeism resulting from back or neck illnesses [24]. In many research investigations, the concept of productivity loss has been employed as a composite measure encompassing both absenteeism, denoting the act of being off-duty from work, and staying longer than usual, which pertains to the effectiveness of work performed by an individual. The reduction in yield is typically quantified as an annual expense and is referred to as an indirect cost [25]. Structured review and meta-synthesis have documented the costs associated with productivity loss in individuals diagnosed with AS. This comprehensive study identified a total of 32 records that specifically examined the issue of productivity loss in AS patients [25]. The study findings indicate that the yearly indirect expenses associated with reduced productivity in individuals with AS who are undergoing biologic treatment vary between 191 USD and 45,954 USD per individual, based on 2013 USD values [25]. Within the meta-analysis, a study was

DOI: https://doi.org/10.54393/pjhs.v5i06.1376

identified that documented a significant drop in indirect costs subsequent to treatment with a biologic medication. Specifically, the study saw a reduction from an initial value of 1968 USD to a post-treatment value of 191 USD [26]. In our investigation, the yearly expenditure associated with LPT amounted to 3817953 ± 132987PKR. This figure is within the spectrum of forgoing documented indirect costs in AS and is similar to the expenses incurred by patients in Korea diagnosed the costs associated with moderate and severe rheumatoid arthritis are 11,085 USD and 13,157 USD, respectively [27]. There are various limitations inherent in this study. Due to the utilization of a prospective cross-sectional study design in this study, the ability to investigate the correlation among factors and patients' reported satisfaction and depletion of productivity was limited. It is important to note that variability in comprehension and interpretation of each item among participants may have been introduced by the utilization of self-reported instruments in this study. Despite the precursory constraints, it is important to highlight the notable positives of this study. This study employed established and verified metrics that have been extensively utilized in previous research. Consequently, this study is a valuable point of reference for comparing results obtained in future studies using the same cohort of participants. Furthermore, this study aims to comprehensively examine the variations in treatment satisfaction, treatment patterns, and expenses associated with Decreased productivity observed in Ankylosing Spondylitis (AS) patients in Pakistan, so contributing to a deeper knowledge of these characteristics within the context of different countries.

CONCLUSIONS

After analysing the data, it was found that out of the four TNF inhibitors currently used to treat In Pakistan, adalimumab is the most commonly prescribed treatment for AS, followed by infliximab. Similar success in regulating disease activity has been seen with the continuous use of adalimumab, usually provided at a modest dose. It seems that adalimumab, even at reduced dosages, can be used in real-world clinical settings and may be sustainable. Among individuals diagnosed with AS, the current TNFi treatment was shown to be quite acceptable. Having said that, happiness was noticeably lower in the treatment convenience domain compared to the other three. Compared to subcutaneous pen injections, subcutaneous syringe and intravenous injections were associated with lower levels of satisfaction. Overall treatment satisfaction might be enhanced by making treatment options more accessible.

Authors Contribution

Conceptualization: MUR
Methodology: AK, HS, FFA, MHL, MFH
Formal analysis: FFA
Writing, review and editing: FFA, MHL, MFH, AN

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Ebrahimiadib N, Berijani S, Ghahari M, Pahlaviani FG. Ankylosing spondylitis. Journal of Ophthalmic & Vision Research. 2021 Jul; 16(3): 462. doi: 10.18502/jovr.v16i3.9440.

[2] Zhu W, He X, Cheng K, Zhang L, Chen D, Wang X *et al.* Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Research. 2019 Aug; 7(1): 22. doi: 10.1038/s41413-019-0057-8.

[3] Arévalo M, Gratacós Masmitjà J, Moreno M, Calvet J, Orellana C, Ruiz D *et al.* Influence of HLA-B27 on the Ankylosing Spondylitis phenotype: results from the Regisponser database. Arthritis Research & Therapy. 2018 Dec; 20: 1-6. doi: 10.1186/s13075-018-1724-7.

[4] Webers C, Ramiro S, Landewé R, van der Heijde D, Van den Bosch F, Dougados M *et al.* Sick leave and its predictors in ankylosing spondylitis: long-term results from the Outcome in Ankylosing Spondylitis International Study. Rheumatic and Musculoskeletal Diseases Open. 2018 Nov; 4(2): e000766. doi: 10.1136/rmdopen-2018-000766.

[5] Proft F and Poddubnyy D. Ankylosing spondylitis and axial spondyloarthritis: recent insights and impact of new classification criteria. Therapeutic Advances in Musculoskeletal Disease. 2018 Jun; 10(5-6): 129-39. doi: 10.1177/1759720X18773726.

[6] Packham J. Optimizing outcomes for ankylosing spondylitis and axial spondyloarthritis patients: a holistic approach to care. Rheumatology. 2018 Nov; 57(6): vi29-34. doi: 10.1093/rheumatology/key200.

[7] Khan MA and Akkoc N. *Ankylosing Spondylitis-Axial Spondyloarthritis.* In: Professional Communications. 2nd Edition. Oxford University Press; 2023. doi: 10.1093/oso/9780198864158.001.0001.

[8] Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. Rheumatology. 2014 Apr; 53(4): 650-7. doi: 10.1093/rheumatology/ket387.

DOI: https://doi.org/10.54393/pjhs.v5i06.1376

[9] Exarchou S, Lindström U, Askling J, Eriksson JK, Forsblad-d'Elia H, Neovius M *et al.* The prevalence of clinically diagnosed ankylosing spondylitis and its clinical manifestations: a nationwide register study. Arthritis Research & Therapy. 2015 Dec; 17: 1-9. doi: 10.1186/s13075-015-0627-0.

[10] Reveille JD, Witter JP, Weisman MH. Prevalence of Axial Spondylarthritis in the United States: estimates from a cross-sectional survey. Arthritis Care & Research. 2012 Jun; 64(6): 905-10. doi: 10.1002/acr.21621.

[11] Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. Rheumatology. 2014 Apr; 53(4): 650-7. doi: 10.1093/rheumatology/ket387.

[12] Braun A, Saracbasi E, Grifka J, Schnitker J, Braun J. Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain? Annals of the Rheumatic Diseases. 2011 Oct; 70(10): 1782-7. doi: 10.1136/ard.2011.151167.

[13] Dagfinrud H, Kjeken I, Mowinckel P, Hagen KB, Kvien TK. Impact of functional impairment in ankylosing spondylitis: impairment, activity limitation, and participation restrictions. The Journal of Rheumatology. 2005 Mar; 32(3): 516-23.

[14] Costello ME, Ciccia F, Willner D, Warrington N, Robinson PC, Gardiner B *et al.* Brief report: intestinal dysbiosis in ankylosing spondylitis. Arthritis & Rheumatology. 2015 Mar; 67(3):686-91. doi: 10.1002/art.38967.

[15] Wen C, Zheng Z, Shao T, Liu L, Xie Z, Le Chatelier E *et al.* Quantitative metagenomics reveals unique gut microbiome biomarkers in ankylosing spondylitis. Genome Biology. 2017 Dec;18: 1-3. doi: 10.1186/s13059-017-1352-6.

[16] Ebringer R, Cooke D, Cawdell DR, Cowling P, Ebringer A. Ankylosing spondylitis: klebsiella and HL-A B27. Reumatologia/Rheumatology. 1977; 16: 190–196. doi: 10.1093/rheumatology/16.3.190.

[17] Videm V, Cortes A, Thomas R, Brown MA. Current smoking is associated with incident ankylosing spondylitis—the HUNT population-based Norwegian health study. The Journal of rheumatology. 2014 Oct; 41(10): 2041-8. doi: 10.3899/jrheum.140353.

[18] Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. New England Journal of Medicine. 2016 Jun; 374(26): 2563-74. doi: 10.1056/NEJMra1406182.

[19] Yates M, Keat A, Gaffney K. Do low-dose anti-TNF regimens have a role in patients with ankylosing spondylitis?. Rheumatology. 2016 May; 55(5): 769-72. doi: 10.1093/rheumatology/kev411.

[20] Acurcio FD, Guerra Junior AA, da Silva MR, Pereira RG, Godman B, Bennie M *et al.* Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. Current Medical Research and Opinion. 2020 Apr; 36(4): 677-86. doi: 10.1080/03007995.2020.1722945.

[21] Lie E, Lindström U, Zverkova-Sandström T, Olsen IC, Forsblad-d'Elia H, Askling J *et al.* Tumour necrosis factor inhibitor treatment and occurrence of anterior uveitis in ankylosing spondylitis: results from the Swedish biologics register. Annals of the Rheumatic Diseases. 2017 Sep; 76(9): 1515-21. doi: 10.1136/annrheumdis-2016-210931.

[22] Walsh JA, Adejoro O, Chastek B, Park Y. Treatment patterns of biologics in US patients with ankylosing spondylitis: descriptive analyses from a claims database. Journal of Comparative Effectiveness Research. 2018 Apr; 7(4): 369-80. doi: 10.2217/cer-2017-0076.

[23] Lee MY, Shin JY, Park SY, Kim D, Cha HS, Lee EK. Persistence of biologic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: an analysis of the South Korean National Health Insurance Database. InSeminars in Arthritis and Rheumatism 2018 Feb; 47(4): 485-491. doi: 10.1016/j.semarthrit.2017.08.007.

[24] Van Der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A *et al.* 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Annals of the Rheumatic Diseases. 2017 Jun; 76(6): 978-91. doi: 10.1136/annrheumdis-2016-210770.

[25] Byun DW, Moon SH, Kim T, Lee HH, Park HM, Kang MI *et al.* Assessment of patient-reported outcomes(PROs): treatment satisfaction, medication adherence, and quality of life (QoL) and the associated factors in postmenopausal osteoporosis (PMO) patients in Korea. Journal of Bone and Mineral Metabolism. 2019 May; 37: 563-72. doi: 10.1007/s00774-018-0956-6.

Oh S, Kim JS, Oh YS, Shin DG, Pak HN, Hwang GS *et al.*

[26] Quality of anticoagulation and treatment satisfaction in patients with non-valvular atrial fibrillation treated with Vitamin K antagonist: result from the Korean atrial fibrillation investigation II. Journal of Korean Medical Science. 2018 Dec; 33(49). doi: 10.3346/jkms.2018.33.e323.

[27] Malinowski KP and Kawalec P. The indirect costs of ankylosing spondylitis: a systematic review and meta-analysis. Expert Review of Pharmacoeconomics & Outcomes Research. 2015 Mar; 15(2): 285-300. doi: 10.1586/14737167.2015.1001370.