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Predictors of not Achieving Remission or Low Disease Activity in Axial Spondyloarthritis Patients from Middle Eastern Countries: A Prospective, Multicenter, Real-world Study

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ABSTRACT

Objectives: We sought to identify the predictors of not achieving remission or low disease activity (LDA) among axial spondyloarthritis (SpA) patients in four Middle Eastern countries. ***Methods***: In this multicenter prospective real-world study, adult patients with axial SpA diagnosed clinically during January–June 2019, and who met the Assessment of SpondyloArthritis International Society classification criteria for axial SpA, were enrolled from the participating centers of four countries—Lebanon, Oman, Qatar, and the UAE. Patient demographics, disease history, comorbidities, treatment, and compliance data were obtained at baseline. The primary outcome was to determine the percentage of patients who did not achieve the clinical target of remission or LDA as indicated by Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) < 2.1 after a three-month follow-up period. Secondary outcomes were assessing the demographic and clinical characteristics of 'achievers' and 'non-achievers' and to study the predictors of ASDAS-CRP ≥ 2.1 in different clinical subsets. ***Results:*** The participants were 309 patients of both sexes, with a median age of 43 years. Women had a slight majority (53.7%). At the end of the study, 72.2% of patients achieved the clinical target of ASDAS-CRP < 2.1. Non-achievers were significantly more likely to have enthesitis, positive human leukocyte antigen B 27 status, psoriasis, peripheral involvement, fibromyalgia, and a lower score on Compliance Questionnaire for Rheumatology (CQR). Multiple regression analysis showed that low CQR score, enthesitis, psoriasis, and family history of SpA were independent predictors of ASDAS-CRP ≥ 2.1. ***Conclusions:*** This real-world study suggests that low compliance, positive human leukocyte antigen B 27 status, peripheral involvement, and presence of enthesitis, psoriasis, and fibromyalgia are predictors of not achieving remission or LDA in axial SpA patients.

Spondyloarthritis (SpA) is a group of interrelated chronic inflammatory diseases with common clinical features, including inflammation of the axial skeleton and peripheral joints, and having a close association with the human leukocyte antigen B27 (HLA-B27).[1] Worldwide prevalence of SpA is 0.2%–2%.[2] In the Middle East, its prevalence has been reported to be as high as 2.2%.[3] The prevalence of HLA-B27 in all SpA patients in the Middle East is in the range of 14%–70%.[4–7]

A growing body of evidence shows that higher disease activity leads to more structural damage in the spine, further lowering the patient's physical functionality, as in the axial form of SpA (axSpA).[8,9] Over the years, biological therapy has improved work productivity and quality of life in axSpA patients.[10] Unlike rheumatoid arthritis, the concept of treat-to-target for axSpA is still debated among rheumatologists.[11–13] However, there is a consensus that treatment should be personalized.[14] In the Middle East there are several challenges that can affect personalized therapeutic decision-making, potentially impacting the achievement of remission or a low disease activity (LDA) status.[15,16]

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The primary objective of this study was to determine the percentage of axSpA patients who achieved remission and LDA (Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) <2.1) after a three-month follow-up period. The secondary objectives were to assess the demographic and clinical characteristics of achievers of remission and LDA compared to non-achievers and to study the predictors of non-achievement (ASDAS-CRP ≥2.1) in different clinical subsets.

METHODS

A multicenter prospective real-world study was conducted among consecutive patients who presented at axSpA consulting rheumatology clinics at tertiary centers in Lebanon, Oman, Qatar, and the UAE.

During the Arab League Against Rheumatism meeting conducted in Oman (2018), a special interest group met to discuss the current needs of SpA patients in the Middle East. Eight rheumatologists from Lebanon, Oman, Qatar, and the UAE expressed interest in participating in a multicenter study to explore the challenges of achieving clinical targets in real-world SpA patients in these countries. The study protocols were reviewed by all investigators and approved by the relevant local institutional review boards or ethics committees.

Consecutive patients who attended the participating centers between January and June 2019, who were clinically diagnosed with axSpA by the rheumatologist, and who met the Assessment of Spondyloarthritis International Society (ASAS) 2009 classification criteria for axSpA, were invited to participate in the study if they were at least 18 years of age and competent to provide informed consent.[17] Patients with only axSpA, and those with axial and concurrent peripheral symptoms but satisfied ASAS classification criteria for axSpA, were included in the study. Those with only peripheral disease were excluded. Since the study aimed to assess only real-life data, the protocol did not require the investigators to change their practice or introduce new treatments except for measuring ASDAS in patients with axial disease after three months of follow-up.

The data and patient consent were collected at the baseline visit of entering the study. All relevant information including patients' demographics, disease history, comorbidities, and previous treatments was noted at baseline and verified by the patients. The outcome measures of ASDAS and compliance questionnaire were conducted at the three-month visit. Since there was no introduction of a new treatment to test, given the short period of follow-up, and having the aim to represent all the centers, the investigators opted for limiting data collection to two occasions —at baseline and three-month visit. The investigators also relied on a single magnetic resonance imaging (taken at the time of the diagnosis) to minimize costs.

At the baseline visit, electronic medical records and patient surveys were used to collect the following data:

1. Patient demographics: current age, age at diagnosis, gender, ethnicity, smoking status, marital status, the highest level of education, insurance coverage, and access to biologics.
2. Disease history: starting date of persistent symptoms; date on which seen by a rheumatologist for the first time; history of clinical features namely, inflammatory low back pain, arthritis, uveitis, enthesitis at any site (based on clinical evaluation), dactylitis, psoriasis, inflammatory bowel disease, preceding genitourinary infection or diarrhea, nail pitting or onycholysis; laboratory features including CRP and HLA-B27 status; radiographic investigations (radiographic sacroiliitis); family history of SpA; and response to non-steroidal anti-inflammatory drugs (NSAIDs).
3. Comorbidities (as reported by the rheumatologist): diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, degenerative lumbar spine disease, osteoarthritis, peptic ulcer disease, fibromyalgia, history of tuberculosis, and malignancy.
4. Compliance Questionnaire for Rheumatology (CQR): the patients filled this self-reported adherence measurement tool created specifically for and validated in rheumatic diseases against electronic medication event monitors, the current gold standard.[18]
5. Treatments: previous and current conventional synthetic disease-modifying drugs (csDMARDs) and biologic DMARDs (bDMARDs) were recorded. The retention rates of treatments received were calculated using the following equation and expressed as a percentage:

[(Ever received – Discontinued) ÷ Ever received] × 100

This real-world study, conducted in four countries, inducted axSpA patients regardless of their disease duration and treatment status; ever received treatment was recorded for analysis.

Patients were followed up for three months. The ASDAS-CRP status was again assessed at the end of that period. ASDAS-CRP < 2.1 was considered as the cut-off point to define achieving clinical target (remission or LDA), while ASDAS-CRP ≥ 2.1 indicated not achieving the target.[19]

The primary outcome was the percentage of patients who achieved remission or LDA (ASDAS-CRP < 2.1) after a three-month follow-up period. Secondary outcomes were identifying the demographic and clinical characteristics of achievers and non-achievers as predictors of different ASDAS-CRP outcomes in different clinical subsets.

Descriptive statistics, student's *t*-test, Mann-Whitney U test, and Fisher's exact test were used for statistical analysis as appropriate. Demographic data and disease and treatment characteristics were described as median and the 25th–75th interquartile range (IQR).

For comparing achievers with non-achievers we used 2 × 2 tables to calculate the odds ratio (OR) and 95% CI of different demographic and clinical variables. Chi-square and Fisher's exact test were used to assess the statistical significance of the association between rows and columns of categorical variables and *t*-test was used for continuous variables.

Multiple regression analysis was used to investigate the impact of different factors on ASDAS-CRP ≥ 2.1, used as a continuous variable, in patients with axSpA. Variables included in the different models tested were selected based on their statistical significance in the univariate analysis, and their clinical relevance. Significant variables were finally isolated using stepwise forward selection described as t-value (coefficient divided by its standard error). All statistical tests were two-sided; $p < 0.050$ was considered statistically significant. Statistical analysis was performed using Minitab version 18.1 software.

The sample size was based on an estimated total study population size of 1200. The confidence level of 95% with a margin of error of 0.050, alpha divided by confidence level was 0.025, and Z-score was 1.95. Based on real-world data, ASAS classification criteria (axSpA total) were met in 85.5% of all patients.[18] Thus, the sample size required to perform the study was estimated at 238.

RESULTS

A total of 309 patients with an established diagnosis of axSpA, who fulfilled the ASAS criteria for axSpA were enrolled from four academic centers and rheumatology clinics in the Middle East. Their median age was 43 years (IQR = 36–51) and 53.7% were women. The median disease duration was six years (IQR = 3.0–9.0). Of the 309 patients, 79.0% had radiographic axSpA and 49.3% had concomitant peripheral features. Criteria of good response to NSAIDs were used in 21.7% of the patients who had been diagnosed with axSpA at the time of initial presentation. At the three-months visit, 72.1% of patients had achieved the clinical target of ASDAS < 2.1. Demographic and clinical features are summarized in Table 1.

Most patients, (223/309; 72.2%) achieved an ASDAS-CRP < 2.1 at three months. On comparing the two groups, patients who did not achieve the clinical target (86/309; 27.8%) were more likely to have enthesitis, a positive HLA-B27 status, psoriasis, concomitant peripheral involvement, or fibromyalgia. They also tended to be less compliant to treatment than those who achieved the clinical target [Table 2]. In addition, the patients who achieved the clinical target were more likely to stay on the drugs csDMARDs and bDMARDs than non-achievers [Table 3]. Otherwise, there was no difference between the two groups regarding demographics, clinical features, and treatment given. We compared the percentage of concomitant peripheral manifestations in the achiever (97/223; 43.5%) and non-achiever (55/86; 64.0%) groups. It was found that the patients with only axSpA had double the chance of achieving the desired ASDAS-CRP < 2.1, compared to those who had both axial and peripheral arthritis ($p = 0.007$) [Table 2]. The latter group of patients formed almost two-thirds of the non-achiever group against fewer than half of the achiever group; the OR of not achieving ASDAS-CRP < 2.1 was 2.3 if the patient had axial and peripheral SpA. This significant difference failed to show in the multivariate model including most of the variables included in the study. As 50.2% of patients had radiographic sacroiliitis, patients

Table 1: Demographic and clinical characteristics of all patients and achievers and non-achievers of the clinical target of Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) < 2.1.

Variables	All patients (N = 309) n (%)	Achievers (n = 223) n (%)	Non–achievers (n = 86) n (%)
Age [median (IQR), years]	43 (36–51)	43 (35–52)	42 (37–51)
Female	166 (53.7)	121 (54.2)	45 (51.9)
Disease duration [median (IQR), years]	6.0 (3.0–9.0)	5.0 (2.0–8.0)	6.0 (2.0–9.0)
Patients with medical insurance/medical coverage	292 (94.5)	212 (95.0)	80 (93.1)
Current smoking	43 (13.9)	27 (12.1)	16 (18.6)
ASDAS-CRP [median (IQR)] ASDAS-CRP [mean]	1.9 (1.5–2.7) 2.1	1.5 (1.3–1.6) 1.5	2.9 (2.3–3.4) 2.9
Arthritis	124 (40.1)	81 (36.3)	43 (50.0)
Dactylitis	42 (13.6)	25 (11.3)	17 (18.5)
Enthesitis	90 (29.1)	53 (22.7)	37 (43.2)
Family history of SpA	57 (18.4)	35 (14.3)	22 (25.9)
HLA-B27	95 (30.8)	57 (25.6)	38 (44.2)
Inflammatory bowel disease	22 (7.1)	16 (7.2)	6 (6.9)
Inflammatory low back pain	212 (68.6)	152 (68.1)	60 (69.8)
Onycholysis	34 (10.9)	24 (10.7)	10 (11.6)
Psoriasis	91 (29.4)	56 (25.1)	35 (40.7)
Sacroiliitis (radiographic) Positive findings in X-ray and MRI	155 (50.2)	111(49.8)	44 (51.1)
Positive findings in MRI not in X-ray	89 (28.8)	65 (29.1)	24 (27.9)
Negative findings in X-ray and MRI	64 (20.7)	46(20.6)	18 (20.9)
Uveitis	19 (6.1)	9 (4.0)	10 (11.6)
Concomitant peripheral manifestations	152 (49.1)	97 (43.5)	55 (63.9)
Comorbidities			
DM	31(10.0)	22 (9.9)	9 (10.4)
Fibromyalgia	49 (15.8)	25 (11.2)	24 (27.9)
Hypertension	55 (17.8)	37 (16.6)	18 (20.9)
IHD+ stroke	9 (3.0)	7 (3.1)	2 (2.3)
Malignancy	3 (1.0)	2 (0.9)	1 (1.2)
Osteoarthritis	62 (20.0)	45 (20.2)	17 (19.7)
Osteoporosis	22 (7.1)	14 (6.3)	7 (8.1)
Hyperlipidemia	25 (8.1)	16 (7.2)	9 (10.4)

IQR: interquartile range; SpA: spondyloarthritis; HLA-B27: human leukocyte antigen B27; MRI: magnetic resonance imaging; DM: diabetes mellitus; IHD: ischemic heart disease.

Table 2: Comparing the non-achievers of clinical targets to achievers.

Variables included in Contingency analysis	Achievers (n = 223) n (%)	Non-achievers (n = 86) n (%)	OR	CI	*p*-value
Enthesitis	50 (22.4)	37 (43.0)	2.7	1.4–5.0	0.002
HLA-B27	54 (25.6)	34 (42.5)	2.0	1.1–3.7	0.030
Psoriasis	56 (25.1)	35 (40.7)	2.1	1.1–3.8	0.020
Concomitant peripheral manifestations	97 (43.5)	55 (63.9)	2.3	1.3–4.0	0.007
Fibromyalgia	25 (11.2)	24 (27.9)	3.1	1.5–6.8	0.003
Unpaired *t*-test	**Difference between means + SE**			**CI**	***p*-value**
Compliance score	-7.5 ± 1.8			-10.9–-4.0	< 0.001

OR: odds ratio; HLA: human leukocyte antigen; SE: standard error.

Table 3: Comparison of treatments received and retention rates between achievers and non-achievers.

Treatment	All patients (n = 309)	Achievers (n = 223)			Non-achievers (n = 86)			*p*-value
		Ever received	Discont-inuation	Retention rate from ever used	Ever received	Discont-inuation	Retention rate from ever used	
Methotrexate	131 (42.4)	96 (43.0)	9(9.4)	87 (90.1)	35 (40.7)	9 (25.7)	26(74.3)	0.005
Salazopyrin	139 (35.6)	80 (35.9)	25 (31.2)	55 (68.8)	59(68.6)	26 (44.1)	33 (55.9)	N.S
Leflunomide	21 (6.8)	14 (6.3)	1 (7.1)	13 (92.9)	7 (8.1)	1 (14.3)	7 (85.7)	N.S
Etanercept	69 (22.3)	45 (20.2)	4 (8.8)	41 (91.1)	25 (27.9)	4 (16.0)	21 (80.4)	0.043
Adalimumab	103 (33.3)	70 (31.4)	5 (7.1)	65 (92.9)	33 (38.4)	6 (18.1)	27 (81.2)	0.040
Infliximab	39 (12.6)	27 (12.1)	2 (7.4)	25 (95.3)	12 (14.0)	1 (8.3)	11(91.7)	N.S
Golimumab	26 (8.4)	10 (4.5)	3 (30)	7 (70.0)	16 (18.6)	6 (37.5)	10 (62.5)	N.S
Secukinumab	12 (3.9)	5 (2.2)	0 (0.0)	5 (100.0)	7 (8.1)	2 (2.3)	5 (71.4)	< 0.001
Certolizumab pegol	23 (7.4)	11 (4.9)	4 (36.4)	7 (63.6)	12 (14.0)	3 (25)	9 (75.0)	N.S

Predictors of Ankylosing Spondylitis Disease Activity Score-C-reactive protein (≥ 2.1. All data are given as n (%). N.S: nonsignificant.

Table 4: Predictors of Ankylosing Spondylitis Disease Activity Score ≥ 2.1 in axial spondyloarthritis (axSpA) patients from the Middle East.

Variables	Coef	SE Coef	95% CI	*p*-value
Compliance score	-0.019	0.004	-0.027–-0.010	< 0.001
Enthesitis	0.308	0.117	0.077–0.539	0.009
Psoriasis	0.276	0.111	0.058–0.493	0.013
Family history of SpA	0.257	0.124	0.013–0.501	0.039

Coef: coefficient; SE Coef: standard error of the coefficient.

with radiographic changes were compared with those without radiographic changes. There was no difference in achieving the target ASDAS on univariate and multivariate analysis. There were no significant differences in treatments received by those who achieved remission/LDA and those who did not.

In this prospective study, low CQR score at baseline ($p < 0.001$), enthesitis ($p = 0.009$), psoriasis ($p = 0.013$), and a family history of SpA ($p = 0.039$) were independent predictors of ASDAS-CRP levels at three months. Demographic, clinical features, radiographic features, CRP lab values, and coexisting comorbidities were not associated with remission/LDA [Table 4].

DISCUSSION

In this real-world, prospective, multicenter study of 309 patients with axSpA from four Middle Eastern countries, 223/309 (72.2%) patients achieved remission or had LDA as per ASDAS-CRP (< 2.1) after a three-months follow-up.

The association of higher disease activity with the presence of concomitant peripheral symptoms has been previously reported by de Winter et al.[20] In his study, patients with both axial and peripheral involvement showed a median ASDAS-CRP level of 3.0 while those with only axial involvement showed 2.6 ($p = 0.014$). The percentage of non-achievers (ASDAS-CRP > 2.1) was higher among those with combined SpA than in those with purely axSpA. Those patients having both axial as well as peripheral SpA showed a higher prevalence of enthesitis than those with axSpA alone (62% vs. 48%; $p = 0.044$).[20]

The results of the de Winter study support the current findings, as 64.0% of our patients with concomitant peripheral symptoms were non-achievers (OR = 2.3; $p = 0.007$). Besides, non-achievers were twice as likely to have enthesitis at three-month review than those who achieved the clinical target. This is consistent with studies with larger cohorts where enthesitis indices were found to significantly correlate with both axial and peripheral joint involvement and higher disease activity, and with a decline in functional capacity and quality of life.[21,22]

Previous studies have shown higher use of biologics among patients with coexisting fibromyalgia

and SpA; a strong association was also seen between multiple switching of biologics and fibromyalgia in patients with SpA.[23] Our study reported a higher prevalence of fibromyalgia among non-achievers than among achievers of clinical targets (24/86; 27.9% vs. 25/223; 11.2 %; $p = 0.004$).

Adherence to therapy is a strong predictor of treatment response.[24] Thus, the low CQR scores found among non-achievers in this study can be considered a predictor of clinical response. In previous studies, non-adherence to biologic therapy was associated with significantly lower response in rheumatic arthritis patients after six months of treatment ($p = 0.013$).[24] Flouri et al,[25] also showed that first-year treatment response predicted long-term drug persistence in patients with SpA who were treated with tumor necrosis factor alpha inhibitors (TNFi).

In our study, among the non-achievers, reduced treatment retention rates were seen for almost all bDMARDs. Higher cost of biological therapies has been suggested as a reason for non-adherence.[26] Access to biologic therapies varies between the Middle Eastern countries. It also depends on the extent of insurance coverage and the recommendations of health providers. However, most patients in our study had medical insurance which covered bDMARD therapies. Hence, cost was an unlikely reason for non-adherence to biologic treatment among our patients. A more plausible reason may be that the bDMARDs, due to their large molecular sizes, are potentially immunogenic.[27] This may cause the body to develop anti-drug antibodies that trigger adverse events, leading to reduced patient compliance.[28] Other studies in rheumatology patients have shown that factors such as current medication type, treatment beliefs, age, race, comorbidities, smoking, clinical status, high disease activity at the time of diagnosis, decreased quality of life, increased body mass index, disease duration, etc. could predict treatment adherence to bDMARDs.[29]

Our study did not report on the immunogenicity of biologics, given the short duration of follow-up. We also did not compare the responses to treatment with anti-TNF inhibitors and IL-17 inhibitors to avoid Type II error as 84.0% of our patients were on anti-TNFs and only 3.9% on IL-17 inhibitors.

AxSpA shows a very strong genetic association with the major histocompatibility complex encoded class I molecule, HLA-B27. It has been postulated that HLA-B27 contributes to ~40% of the overall risk for axSpA.[30] In our study, only 30.8% of patients were HLA-B27 positive. Of these, 42.5% were non-achievers of clinical targets. Our result corroborates the relatively weak association of HLA-B27 seen in Middle Eastern patients (25–75%) compared to their Western European counterparts (> 90%).[5,6,31]

Studies have shown that patients with shorter disease duration and better functional status benefit more from TNF-blockers.[32] Supporting this, a longer disease duration of 7.5 years was seen among the non-achievers in our study, albeit without statistical significance.

Very little data exists regarding axSpA patient populations in the Middle East. Since our study included people of mostly Arab ethnicity from four countries in the region, these findings can be applied for the management of SpA in the Middle East. Another strength of our study is the larger sample size compared to other similar studies. In addition, the consecutive patient sampling method in our study eliminated the risk of selection bias. In the absence of regional registries, the present results throw light on the region-specific demographic and clinical features of axSpA and may assist in devising appropriate management strategies.

A limitation of this study is that it was conducted only at tertiary centers. While conducting the research in four countries is a strength, it can also be argued to be a limitation. The Middle East is a vast region with large countries such as Saudi Arabia and Egypt which our study did not include. The solution is to expand the study to cover more countries in the region. There was no agreement between researchers to use the classification criteria to classify those patients with fibromyalgia. The researchers relied on clinical diagnosis documents in patients' medical record to classify this comorbidity. Additionally, the short follow-up duration of three months was insufficient to allow proper reporting of extra-musculoskeletal features of SpA that could develop years later (e.g., uveitis).

CONCLUSION

In our study, 72.2% of axSpA patients achieved the clinical target of remission and LDA (ASDAS-CRP < 2.1) at three months of follow-up. Enthesitis, psoriasis, positive HLA-B27 status, concomitant

peripheral involvement, coexisting fibromyalgia, and reduced CQR score were more likely to be associated with non-achievers of clinical targets. Low CQR score, enthesitis, psoriasis, and family history of SpA were independent predictors of non-achievement (ASDAS-CRP ≥ 2.1). The presence of these identified predictors should alert rheumatologists about the need for closer monitoring and intensive follow-up to reach optimal clinical targets.

Disclosure
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