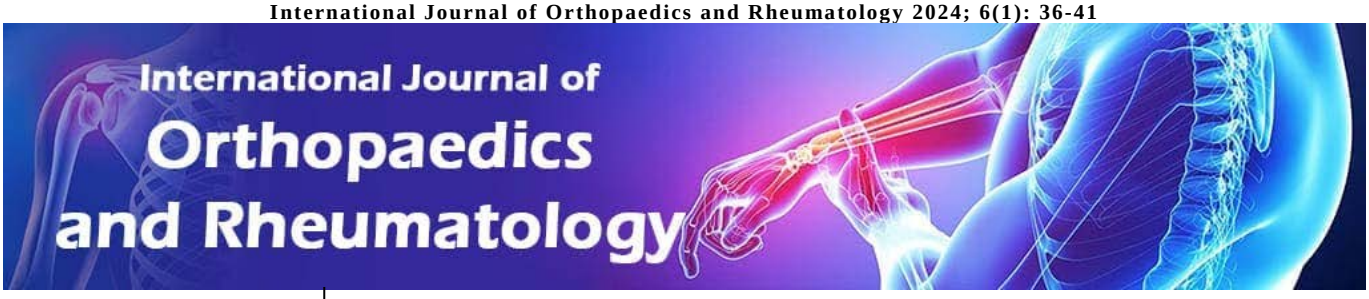

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Efficacy, safety and predictors of response to Adalimumab in treatment of patients with active ankylosing spondylitis

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Abstract
Background: Ankylosing Spondylitis is a spondyloarthritide that causes spinal joint inflammation and bone fusion. Ankylosing Spondylitis produces axial skeleton ankylosis and is the prototype of Spondyloarthritides. Ankylosing Spondylitis has no cure, however therapies and drugs can lessen pain, stiffness, and quality of life. Adalimumab, a human monoclonal IgG1 antibody used to neutralise TNF-α, has shown beneficial in treating Ankylosing Spondylitis in recent years.
Objective: To evaluate the efficacy and safety of Adalimumab in patients with active Ankylosing Spondylitis (AS) and to identify predictors of response to treatment.
Methods: A single-group prospective study over 17 months involving 61 Iraqi patients with AS diagnosed by the Modified New York criteria (1984). Patients received Adalimumab 40 mg subcutaneously every two weeks. Disease activity was assessed using BASDAI, and function using BASFI at baseline, 3 months, and 6 months. Predictors of response, including age, gender, disease duration, HLA-B27, smoking, steroid use, DMARDs, and prior biologics use, were analyzed.
Results: BASDAI 50% response rate was 59% at 3 months, increasing to 85.6% at 6 months. Age ($p=0.026$) and prior biologics use ($p=0.016$) were significant predictors of response, with older age and prior biologics use associated with reduced response. BASFI ≥5 group showed a significant reduction in scores by 2 units at 3 months and 2.5 units at 6 months. In the BASFI <5 group, reductions were insignificant. WBC count reduction was moderately strong (Cohen's $d=0.43$), while effects on Hb, AST, ALT, blood urea, and serum creatinine were weak.
Conclusion: Adalimumab is effective and safe in treating active AS. Age and prior biologics use significantly correlate with reduced treatment response.

Keywords: Efficacy, safety, predictors, response, adalimumab, treatment, active ankylosing spondylitis

Introduction
Ankylosing Spondylitis (AS) is the prototype of a group of interrelated diseases called spondyloarthritides (SpA), which includes psoriatic arthritis, arthritis associated with inflammatory bowel disease, and reactive arthritis. These diseases share common clinical features and a strong genetic association with HLA-B27 [1]. AS is a chronic, progressive inflammatory disease that primarily affects the axial skeleton and, to a lesser extent, peripheral joints, eyes, gut, and cardiovascular system. It is characterized by disabling inflammatory back pain due to sacroiliitis and spondylitis [1]. The prevalence of SpA ranges from 0.6% to 1.9%, with AS affecting approximately 0.5% of the population [2]. In northern Norway, the incidence was 7.26 per 100,000 over 34 years, while in Greece and Japan, it was significantly lower due to the lower prevalence of HLA-B27 [3]. AS is more common in men, with a male-to-female ratio of 2:1, though earlier studies underdiagnosed AS in women [4]. Approximately 95% of Asian AS patients are HLA-B27 positive, compared to 78–92% in Western populations [5]. The exact etiology of AS is unclear, though a strong genetic component is evident, with HLA-B27 being the strongest associated factor [6]. Proposed theories include genetic predisposition, with over 20 HLA-B27 allotypes, and environmental factors like a potential link to Klebsiella [7]. Pathophysiology involves progressive inflammation leading to fibrosis and ankylosis of the sacroiliac joints (SIJs) and spine. Enthesitis, characterized by inflammation at the insertion of tendons, precedes calcification

and bone formation, leading to syndesmophytes and vertebral fusion [7]. AS is diagnosed based on clinical criteria such as inflammatory back pain, enthesitis, and arthritis, supported by radiographic findings. The Modified New York criteria (1984) and the ASAS criteria for axial SpA are commonly used, with sensitivity and specificity ranging from 83% to 97% [8]. Laboratory tests, including HLA-B27, elevated ESR, and CRP, may assist in diagnosis but are not definitive [7]. Radiographs of the SIJs and spine often show characteristic changes such as pseudo-widening and sclerosis as the disease progresses [7]. AS treatment focuses on symptom control and exercise to minimize deformity. NSAIDs, particularly indomethacin, are commonly used, while TNF inhibitors, such as Adalimumab, are highly effective in reducing inflammation and improving function [9]. Other biologics like anti-IL-17 therapies show promise, while corticosteroids are reserved for local injections [9]. Adalimumab is a fully human monoclonal antibody targeting TNF-α, licensed for AS treatment by the FDA in 2006 [10]. It improves disease activity and function, with a favorable safety profile, as demonstrated in the ATLAS trial and subsequent studies [5, 11]. The aims of this study were: To assess the efficacy and safety of Adalimumab in patients with active ankylosing spondylitis. To assess the predictors of response to Adalimumab in treatment of patients with active ankylosing spondylitis.

Methods

This was an open-label, single-group prospective study conducted over 17 months on Iraqi patients with Ankylosing Spondylitis (AS) attending the Rheumatology Clinic at Baghdad Teaching Hospital from October 2014 to March 2016. Patients were included if they met the Modified New York criteria (1984) for AS diagnosis, had a Bath Ankylosing Spondylitis Functional Index (BASFI) ≥ 4, and were on ongoing treatment with NSAIDs, DMARDs, or corticosteroids. Exclusion criteria included patients under 16 years, those with overlapping inflammatory diseases, recent infections, or neurological symptoms suggestive of demyelination. A total of 61 patients met the criteria, but 10 were lost to follow-up, leaving 51 who completed the study.

All patients received Adalimumab 40 mg subcutaneously every other week. Baseline demographic, medical, and laboratory data were collected at the first visit, including age, sex, disease duration, prior medications, and HLA-B27 status. Lab tests for hemoglobin, WBC count, AST, ALT, urea, and creatinine were performed at baseline and during follow-up at 3 and 6 months. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and functional status using the BASFI. Data were analyzed using IBM SPSS version 23. Categorical variables were analyzed by cross-tabulation and Chi-square tests. The Kaplan-Meier method was used to calculate the incidence rate of selected outcomes. The Cox-regression model analyzed dichotomous outcomes, allowing for time-dependent variables and losses to follow-up. Paired t-tests assessed the significance of mean differences over time. Effect size was calculated using Cohen's d, with a small effect defined as <0.3, medium as 0.3-0.7, and large as ≥0.8. An alpha level of 0.05 was used for statistical significance.

Results

This chapter presents the analysis of 61 patients diagnosed with Ankylosing Spondylitis (AS), with ages ranging from 18 to 58 years (mean 35±8.9 years). The disease duration ranged from 40 days to 30 years (mean 6.7±6.9 years). The majority of patients were male (86.9%) and 18% were smokers. Positive HLA-B27 status was found in 65.6% of participants. Prior biologic agent use (Infliximab, Etanercept) was reported in 39.3%, steroid use in 24.6%, and DMARDs use (Methotrexate, Salazopyrine) in 13.1%. All patients followed a treatment plan with Adalimumab, with 51 completing the 6-month study period. A total of 10 patients discontinued treatment after the first and third months. Disease activity was assessed using the BASDAI index, aiming to reduce disease activity, while functional status was measured by BASFI. Participants with high BASFI scores (≥5) were analyzed separately from those with low scores (<5) to assess changes in functional disability. The treatment goal for high BASFI patients was to reduce disability, while for low BASFI patients, the aim was to maintain low functional status. As in tables 1.

Table 1: The study sample's frequency distribution by gender, smoking propensity, and positive HLA-B27 marker. The relative frequency of the use of specific substances in treatment in the past and present. The frequency distribution of the study sample by the time of treatment change or follow-up discontinuation (months) for study participants.

	N	%
Gender		
Female	8	13.1
Male	53	86.9
Total	61	100.0
Smoking habit		
Never smoked	50	82.0
Current smoker	11	18.0
Ex-smoker	0	0.0
Total	61	100.0
HLA-B27		
Negative	21	34.4
Positive	40	65.6
Total	61	100.0
History of using Biological drugs	24	39.3
Using Steroid	15	24.6
Using DMARDS	8	13.1

The objective of this study was to reduce disease activity in participants with high BASDAI scores (≥ 4) to a low disease activity level, targeting a 50% reduction in BASDAI scores (BASDAI 50). Survival analysis accounted for losses to follow-up at different intervals. As shown in Table 2, the response rate for achieving BASDAI 50 was 59% after three months of treatment, increasing to 85.6% after six months. A Cox-regression model was used to assess the independent effects of age, gender, disease duration, HLA-B27 status, smoking, DMARDs use, steroid use, and prior use of biologic agents on treatment response. Age and prior biologic use showed statistically significant associations with treatment response. Specifically, for each one-year increase in age, the likelihood of response decreased by 4%. Additionally, prior use of biologic agents reduced the likelihood of response by 2.5 times. Although not statistically significant, male gender, DMARDs, and steroid use were associated with an increased likelihood of

response, while positive HLA-B27 status was linked to a reduced likelihood of response (Table 3). As shown in Tables 4 and 5, the BASDAI score showed a significant reduction of 1.4 units after three months of treatment and 2 units after six months, compared to baseline. These treatment effects were statistically significant and were considered strong (Cohen's d > 0.8).

Table 2: Kaplan-Meier survival analysis for the risk of positive response to treatment measured by 50% reduction compared to its baseline BASDAI score.

Follow up time (Months after starting treatment)	Cumulative incidence rate at the end of follow up interval
3	59.0
6	85.6

Table 3: Cox-regression model with the risk of positive response to treatment measured by 50% reduction compared to its baseline BASDAI score as the outcome variable and selected explanatory variables included in the model.

	P	Partial OR	95% confidence interval for OR
Age (Years)	0.088	0.96	(0.91 to 1.01)
Male gender compared to female	0.78 [NS]	1.25	(0.27 to 5.78)
Duration of the disease (Years)	0.5 [NS]	1.02	(0.96 to 1.09)
Positive HLA-B27	0.31 [NS]	0.67	(0.31 to 1.45)
Being a smoker compared to non-smoker	0.63 [NS]	1.26	(0.5 to 3.18)
Using DMRADs	0.35 [NS]	1.64	(0.58 to 4.64)
Using steroids	0.8 [NS]	1.12	(0.46 to 2.74)
History of using Biologic agents	0.057	0.41	(0.16 to 1.03)

P (Model) = 0.17 [NS]

Table 4: The change in BASDAI 50% score after three months of treatment compared to pretreatment (Baseline) level

BASDAI score	Baseline	After 3 months of treatment	changes after 3 months compared to baseline	Cohen's d	P
Range	(4 to 9.8)	(0.4 to 9)	(-7.8 to 4.9)	-0.84	<0.001
Mean	6.6	5.2	-1.4		
SD	1.5	1.8	2.2		
SE	0.21	0.25	0.3		
N	56	56	56		

Table 5: The change in BASDAI 50% score after six months of treatment compared to pretreatment (Baseline) level

BASDAI score	Baseline	After 6 months of treatment	Changes after 6 months compared to baseline	Cohen's d	P
Range	(4 to 9.8)	(0 to 9.8)	(-8.4 to 5.7)	-1.03	<0.001
Mean	6.7	4.7	-2		
SD	1.5	2.3	2.6		
SE	0.22	0.33	0.38		
N	51	51	51		

The objective of treatment in this group was to reduce the functional status score (BASFI ≥5) to below 5. Survival analysis showed that 69.6% of participants achieved this goal after three months of treatment, increasing to 78.9% after six months. A Cox-regression model revealed that age and positive HLA-B27 status had a statistically significant impact on treatment response, with older age reducing the likelihood of a favorable response by 4% per year, and positive HLA-B27 status reducing the likelihood by twofold.

Table 6: Kaplan-Meier survival analysis for the risk of positive response to treatment measured by low BASFI score < 5 among subjects with high BASFI ≥5.

Follow up time (Months after starting treatment)	Cumulative incidence rate at the end of follow up interval
3	69.6
6	78.9

Table 7: Cox-regression model with the risk of positive response to treatment measured by low BASFI score <5 as the outcome variable and selected explanatory variables included in the model among subjects with high BASFI ≥5

	P	Partial OR	95% confidence interval for OR
Age (Years)	0.09	0.96	(0.91 to 1.01)
Male gender compared to female	0.25 [NS]	0.46	(0.13 to 1.7)
Duration of the disease (Years)	0.83 [NS]	0.99	(0.94 to 1.05)
Positive HLA-B27	0.057	0.48	(0.23 to 1.02)
Being a smoker compared to non-smoker	0.61 [NS]	0.77	(0.28 to 2.11)
Using DMRADs	0.77 [NS]	1.18	(0.4 to 3.45)
Using steroids	0.57 [NS]	1.28	(0.54 to 3.02)
History of using Biologic agents	0.58 [NS]	0.81	(0.38 to 1.73)

P (Model) = 0.26[NS]

Table 8: The change in BASFI score after three months of treatment compared to pretreatment (Baseline) level among subjects with high BASFI score ≥5

BASFI score	Baseline	After 3 months of treatment	Changes after 3 months compared to baseline	Cohen's d	P
Range	(5 to 9.9)	(0 to 9)	(-8.8 to 1.5)	-1.26	<0.001
Mean	6.7	4.7	-2		
SD	1.2	1.9	2.1		
SE	0.17	0.28	0.31		
N	45	45	45		

Table 9: The change in BASFI score after six months of treatment compared to pretreatment (Baseline) level among subjects with high BASFI score ≥5

BASFI score	Baseline	After 6 months of treatment	Changes after 6 months compared to baseline	Cohen's d	P
Range	(5 to 9.9)	(0 to 7.8)	(-9.2 to 2.2)	-1.46	<0.001
Mean	6.7	4.1	-2.5		
SD	1.2	2.1	2.4		
SE	0.18	0.32	0.37		
N	42	42	42		

Although not statistically significant, male gender and prior use of biologic drugs were associated with a lower likelihood of response, while DMARDs and steroids increased the response likelihood. Compared to baseline, the BASFI score showed a significant reduction of 2 units after three months and 2.5 units after six months of treatment, with all treatment effects being statistically significant and evaluated as strong (Cohen's d > 0.8). Tables (6-9). The objective of treatment in this group is to maintain the low functional status among study participants with an already low functional score (BASFI score<5) at a low functional status. As shown in table 10 and 11, compared to pre-treatment level, the BASFI score showed a small and statistically insignificant reduction by a mean of 0.5 units after three months and 0.6 units after the full six months of treatment. All the treatment effects were statistically insignificant and were evaluated as a weak to moderate effect.

Table 10: The change in BASFI score after three months of treatment compared to pretreatment (baseline) level among subjects with low BASFI score <5.

BASFI score	Baseline	after 3 months of treatment	Changes after 3 months compared to baseline	Cohen's d	P
Range	(1.6 to 4.8)	(1.4 to 4.5)	(-2.5 to 1.6)	-0.48	0.37 [NS]
Mean	3.1	2.7	-0.5		
SD	1	1.1	1.6		
SE	0.3	0.34	0.48		
N	11	11	11		

Table 11: The change in BASFI score after six months of treatment compared to pretreatment (baseline) level among subjects with low BASFI score <5.

BASFI score	Baseline	After 6 months of treatment	Changes after 6 months compared to baseline	Cohen's d	P
Range	(1.6 to 4.2)	(0 to 7)	(-4.2 to 4.9)	-0.3	0.52 [NS]
Mean	3.1	2.4	-0.6		
SD	0.9	2.7	2.9		
SE	0.29	0.91	0.96		
N	9	9	9		

Discussion

For many years, NSAIDs were the primary pharmacological treatment for Ankylosing Spondylitis (AS), improving clinical symptoms in 70–80% of patients [12]. However, newer treatment options have been developed for those who do not respond adequately to NSAIDs [13]. To our knowledge, this is the first study to evaluate the efficacy and safety of Adalimumab in AS patients in Iraq. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) are commonly used tools for assessing disease activity and function in AS patients [14]. These indices are highly correlated, and previous studies have shown that disease activity is a major factor in the deterioration of physical function [15, 16]. In our study, the BASDAI 50% response rate was 59% after three months of Adalimumab treatment, increasing to 85.6% after six months, which is consistent with findings from Rudwaleit M *et al.* [17], who reported a 57.2% response rate after 12 weeks of Adalimumab in a large multinational study of 1250 patients. Similarly, Kobayashi S *et al.* [18] reported that 65.9% of patients achieved a 50% improvement in BASDAI after 12 weeks, with sustained responses through 60 weeks. Our study found that age and prior biologic use were significantly associated with reduced treatment response. Specifically, each one-year increase in age was associated with a 4% decrease in the likelihood of response, while prior use of biologic agents reduced the likelihood of response by 2.5 times. These findings align with Rudwaleit M *et al.* [19], who reported that younger age is a key predictor of response to TNF blockers. Glintborg B *et al.* [20] also found that patients who switched biologics had lower response rates and shorter treatment durations. The reduced response in older patients may be explained by age-related physiological and immunological changes, as well as longer disease duration and the presence of comorbidities, which can

negatively impact treatment outcomes [21, 22]. Similarly, the reduced response in patients with prior biologic use may be due to the formation of antibodies against TNF-α blockers [20, 23]. Regarding functional improvement, our study is the first to compare Adalimumab's efficacy between patients with high (BASFI ≥5) and low (BASFI <5) functional scores. In the BASFI ≥5 group, the response rate was 69.6% after three months and 78.9% after six months, with a significant reduction of 2.5 units in BASFI scores after six months. These findings are consistent with those of Van der Heijde D *et al*. [24], who reported that Adalimumab therapy can lead to rapid and sustained improvement in AS patients with total spinal ankylosis. In contrast, patients in the BASFI <5 group showed statistically insignificant reductions in BASFI scores, suggesting that Adalimumab may be more effective in patients with higher baseline functional impairment. Although male gender, smoking, and prior biologic use were associated with reduced treatment response, these factors were not statistically significant. Use of conventional DMARDs and steroids was associated with an increased likelihood of response, but this effect was also not significant. These findings highlight the complexity of predicting treatment outcomes in AS patients and the need for further research to identify reliable predictors of response. In terms of safety, our study found no significant changes in hemoglobin, WBC count, liver enzymes (AST, ALT), blood urea, or serum creatinine levels after six months of Adalimumab treatment. These results are consistent with previous studies [5, 25, 26], which found that Adalimumab was generally well-tolerated and did not result in clinically significant laboratory changes. However, rare cases of renal impairment have been reported in AS patients treated with Adalimumab [27, 28], underscoring the importance of monitoring renal function in these patients. Current study supports the efficacy and safety of Adalimumab in Iraqi AS patients, particularly in younger patients and those without prior biologic use. Further research is needed to explore the long-term effects of Adalimumab and to identify additional predictors of treatment response.

Conclusion

Adalimumab drug is effective and relatively safe in treatment of patients with active ankylosing spondylitis. Increase in age, positive history of using of other biological drugs and positive Human leukocyte antigen-subtype B27 had significant correlation with reduced response to treatment.

Conflict of Interest

Not available

Financial Support

Not available

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