Raised Inflammatory Markers as Predictors of Response to Anti-tumor Necrosis Factor Drugs (etanercept and infliximab) in a Sample of Iraqi Patients with Ankylosing Spondylitis

Saif Abdulkareem Raoof Al-Shaibani[1], Nizar Abdullatif Jassim[2], Anmar Abdulwahhab Khaleel Al-Bayati[3]

[1]Department of Medicine, Baaquba Teaching Hospital, Diyala, Iraq, [2]Department of Medicine, Baghdad Teaching Hospital, Baghdad, Iraq, [3]Department of Medicine, Merjan Teaching Hospital, Babil, Iraq

Abstract

Background: Ankylosing spondylitis (AS) is a chronic systemic inflammatory disorder mainly affecting the axial skeleton, although peripheral joints, entheses, and extra-articular tissues such as eyes, heart, and lungs may also be involved. Raised inflammatory markers in patients with AS at the start of anti-tumor necrosis factor (anti-TNF) therapy are associated with more clinical response. **Objectives:** The aim of this article is to assess the role of raised inflammatory markers in predicting response to anti-TNF drugs in patients with AS. **Materials and Methods:** The prospective cohort study enrolled a total of 71 patients with AS. Nineteen patients were excluded from the study due to discontinuation of anti-TNF therapy and 52 patients continued in the study and were followed for 3 months. **Results:** The mean age of the patients was 35.2±9.6 years, males constitute 84.6% of them and the median disease duration was 5 (3–10) years. Univariate analysis showed that the predictors of response to anti-TNF drugs were raised baseline C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Bath Ankylosing Spondylitis Disease Activity Index, and Bath Ankylosing Spondylitis Functional Index. Multivariate analysis showed that the only independent predictor for response to anti-TNF drugs was raised baseline CRP. The optimal cut point for CRP to predict response was >7.5 mg/L, whereas that for ESR was >32 mm/h. **Conclusion:** Raised inflammatory markers at baseline predict better response to anti-TNF drugs in AS patients. CRP had better prediction of response to anti-TNF drugs than ESR.

Keywords: Ankylosing spondylitis, inflammatory, Iraq, tumor necrosis factor

Introduction

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disorder mainly affecting the axial skeleton, although peripheral joints, entheses, and extra-articular tissues may also be involved, such as eyes, heart, and lungs.[1]

The prevalence of AS varies worldwide from 0 to 1.8% and is highest in northern European populations and lowest in sub-Saharan Africa.[2] AS is more common in males, with a male: female ratio of 2:1 to 3:1.[3] The peak age of onset is in the second and third decades of life.[4] The estimated prevalence of AS in Iraq is 0.07%; 84% of Iraqi patients with AS are HLA-B27-positive, whereas 2.1% of healthy Iraqi populations are HLA-B27-positive.[5]

Access this article online

Quick Response Code:

Website: www.medjbabylon.org

DOI: 10.4103/MJBL.MJBL_27_21

Raised inflammatory marker levels including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) might identify patients with more active disease who are more likely to benefit from anti-tumor necrosis factor (TNF) treatment than patients with chronic, less active disease.[6] Several studies concluded that raised inflammatory markers (CRP or ESR) in patients with AS at the start of anti-TNF therapy are associated with more clinical response.[7-9]

Address for correspondence: Dr. Anmar Abdulwahhab Khaleel Al-Bayati, Department of Medicine, Merjan Teaching Hospital, Babil, Iraq.
E-mail: anmar_albayaty@yahoo.com

Submission: 20-April-2021 **Accepted:** 29-July-2021
Published Online: 29-September-2021

How to cite this article: Al-Shaibani SR, Jassim NA, Al-Bayati AK. Raised inflammatory markers as predictors of response to anti-tumor necrosis factor drugs (etanercept and infliximab) in a sample of Iraqi patients with ankylosing spondylitis. Med J Babylon 2021;18:241-4.

The aim of this study is to assess the role of raised inflammatory markers (CRP and ESR) in predicting response to anti-TNF drugs in patients with AS.

Patients and Methods

Study design and population

A prospective cohort study was conducted at the Rheumatology Unit in Baghdad Teaching Hospital during the period between September 2016 and June 2017.

A total of 71 Iraqi patients with AS were enrolled in the study; all of them were fulfilling the modified New York criteria for AS[10] and ASAS classification criteria for diagnosing spondyloarthropathy.[11] Nineteen patients were excluded from the study due to discontinuation of anti-TNF therapy and 52 patients continued in the study and were followed for 3 months.

Ethical issue, approval, and official permission

Prior to data collection, a signed consent from each of the participants was obtained after explaining the purpose of the study and ensuring privacy of the data.

The study protocol was reviewed; approval and official permission were obtained from the Ministry of Higher Education and Scientific Research, Baghdad University, College of Medicine to conduct the present study.

Methods

The following data were obtained using data sheet:

1. *Sociodemographic data*: include name, age, gender, weight (in kg), height (in m), body mass index (BMI), and smoking status.
2. *Clinical data*: include disease duration from onset of symptoms, current treatment and presence of peripheral arthritis, enthesitis, or uveitis.
3. *Disease activity*: evaluated at baseline and after 3 months of treatment with anti-TNF drugs by using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[12] The response to anti-TNF drugs is determined by improvement in BASDAI ≥ 2 score from baseline till 3 months.[13]
4. *Functional status*: This is evaluated at baseline and after 3 months of treatment with anti-TNF drugs by using Bath Ankylosing Spondylitis Functional Index (BASFI).[14]
5. *Investigation data*: These include baseline CRP, ESR, white blood cell (WBC), Hb, and platelets.

Statistical analysis

The Anderson darling test was done to assess whether continuous variables follow normal distribution; if they follow normal distribution, then mean and standard deviation are used, and if they did not follow normal distribution, then median and interquartile range will be used to present the data. Discrete variables are presented using number and percentage to present the data; the χ^2 test is used to analyze the discrete variable or Fisher's exact test is used to analyze the distribution between two groups. Two samples *t*-test was used to analyze the differences in means between the two groups. Mann–Whitney *U*-test was used to analyze the differences in median of the two groups. Binary logistic regression analysis was used to calculate odds ratio (OR) and their 95% confidence intervals, when the outcome can be categorized into two binary levels.

Receiver operating characteristics (ROCs) are used to see the validity of different parameters in separating cases with responders from non-responders. The trapezoidal method was used to calculate the curve.

SPSS 20.0.0, Minitab 17.1.0, MedClac 14.8.1, and GraphPad Prism 7.0 software package are used to make the statistical analysis; *P*-value is considered when appropriate to be significant if it is less than 0.05.

Results

The study included 52 patients with AS: 28 of them were receiving etanercept and 24 were receiving infliximab. There was no significant difference between patients in the infliximab and etanercept groups in their demographic variables, disease duration, response, use of drugs, and presence of peripheral arthritis, enthesitis, or uveitis as illustrated in Tables 1 and 2.

In the univariate analysis, four variables were predictors of good response in all subjects which are raised baseline BASDAI, BASFI, ESR, and CRP. In patients receiving etanercept, three variables were the predictors of good response which are raised baseline BASDAI, ESR, and CRP. In the infliximab-receiving patients, two variables were the predictors of good response which are raised baseline ESR and CRP, as illustrated in Table 3.

Table 1: Demographic variables of AS patients according to therapy

	Etanercept	Infliximab	All	*P*-value
Number	28	24	52	—
Age in years, mean±SD	35.8 ± 10.8	34.5 ± 8.1	35.2 ± 9.6	0.626
BMI, mean±SD	27.1 ± 3.9	28.1 ± 7.1	27.6 ± 5.6	0.544
Gender				1.0
Female	4 (14.3%)	4 (16.7%)	8 (15.4%)	
Male	24 (85.7%)	20 (83.3%)	44 (84.6%)	
Disease duration, years	5 (2–10)	6 (3–10)	5 (3–10)	0.580
Smoking				0.938
Negative	13 (46.4%)	10 (41.7%)	23 (44.2%)	
Ex-smoker	3 (10.7%)	3 (12.5%)	6 (11.5%)	
Active	12 (42.9%)	11 (45.8%)	23 (44.2%)	

BMI = body mass index; probability value < 0.05

In the multivariate analysis, only raised baseline CRP remained an independent predictor of response after 3 months of anti-TNF therapy, as illustrated in Table 4.

CRP had better prediction of 3 months response than ESR with an optimal cut point of >7.5 mg/L for CRP (and >32 mm/h for ESR), as illustrated in Table 5.

Table 2: Disease characteristics and use of drugs in patients according to therapy

		Etanercept	Infliximab	All	*P*-value
Number		28	24	52	—
Response	Yes	19 (67.9%)	16 (66.7%)	35 (67.3%)	0.927
	No	9 (32.1%)	8 (33.3%)	17 (32.7%)	
NSAID use	Yes	17 (60.7%)	18 (75.0%)	35 (67.3%)	0.274
	No	11 (39.3%)	6 (25.0%)	17 (32.7%)	
DMARD use	Yes	3 (10.7%)	3 (12.5%)	6 (11.5%)	1.0
	No	25 (89.3%)	21 (87.5%)	46 (88.5%)	
Steroids use	Yes	1 (3.6%)	1 (4.2%)	2 (3.8%)	1.0
	No	27 (96.4%)	23 (95.8%)	50 (96.2%)	
Peripheral arthritis	Yes	4 (14.3%)	4 (16.7%)	8 (15.4%)	1.0
	No	24 (85.7%)	20 (83.3%)	44 (84.6%)	
Enthesitis	Yes	12 (42.9%)	8 (33.3%)	20 (38.5%)	0.482
	No	16 (57.1%)	16 (66.7%)	32 (61.5%)	
Uveitis	Yes	0 (0.0%)	3 (12.5%)	3 (5.8%)	0.092
	No	28 (100.0%)	21 (87.5%)	49 (94.2%)	

NSAID = non-steroidal anti-inflammatory drugs; DMARD = disease-modifying anti-rheumatic drugs; probability value < 0.05

Discussion

This study showed in the univariate analysis that patients with raised baseline CRP and ESR had better response to anti-TNF drugs after 3 months of therapy than those with normal CRP and ESR. This agrees with the results of Arends *et al.*[7] and Lord *et al.*[8] Whereas in the multivariate analysis, only a raised baseline CRP value remained an independent predictor of response to anti-TNF drugs in AS patients. This is close to the results of Rudwaleit *et al.*'s study,[15] which showed that raised baseline CRP is associated with better response.

The optimal cut point of CRP to predict response to anti-TNF drugs is >7.5 mg/L. This disagrees with the results of Glintborg *et al.*'s study,[6] which concluded that AS patients responded to anti-TNF when the baseline CRP was >14 mg/L. This difference may be due to different laboratory processes, disease activity, or genetic components.

This study also showed that raised BASDAI and BASFI at baseline can predict response to anti-TNF drugs. This partially disagrees with the result of Rudwaleit *et al.*'s study,[9] which showed that raised BASDAI and low BASFI at baseline predict better response to anti-TNF drugs. This difference may be attributed to the fact that BASFI depends only on patients' evaluation of limitation in daily activities, and this limitation occurs either due to pain from active disease which responds to treatment

Table 3: Univariate logistic regression analysis for predictors of response to anti-TNF drugs in AS patients according to therapy

	All			Etanercept			Infliximab		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	0.981	0.923–1.042	0.528	0.960	0.890–1.035	0.286	1.024	0.919–1.141	0.665
Gender (male)	0.644	0.116–3.590	0.616	0.667	0.059–7.475	0.667	0.619	0.054–7.121	0.700
BMI, kg/m^2	0.995	0.896–1.105	0.926	1.068	0.868–1.314	0.534	0.971	0.858–1.098	0.637
Smoking									
Negative	1.821	0.521–6.370	0.348	1.125	0.209–6.046	0.891	3.333	0.473–23.471	0.227
Ex-smoker	1.286	0.194–8.534	0.795	1.0	0.068–14.640	1.0	1.667	0.115–24.256	0.708
Smoker	1.0	—	0.644	1.0		0.990	1.0		0.481
Disease duration	1.012	0.906–1.131	0.830	1.060	0.888–1.264	0.521	0.983	0.853–1.132	0.807
BASDAI baseline	**7.213**	**1.832–28.400**	**0.005**	**6.282**	**1.137–34.713**	**0.035**	10.263	0.843–124.941	0.068
BASFI baseline	**1.648**	**1.058–2.567**	**0.027**	1.581	0.833–3.003	0.161	2.047	0.967–4.337	0.061
NSAID	2.568	0.760–8.674	0.129	2.708	0.529–13.855	0.232	2.6	0.387–17.451	0.325
DMARD	0.968	0.159–5.889	0.972	0.194	0.015–2.501	0.209	—	—	—
ESR, mm/h	**1.073**	**1.028–1.121**	**0.001**	**1.063**	**1.008–1.122**	**0.025**	**1.090**	**1.012–1.174**	**0.022**
CRP, mg/L	**1.242**	**1.104–1.398**	**<0.001**	**1.245**	**1.060–1.463**	**0.008**	**1.244**	**1.042–1.486**	**0.016**
WBC	1.109	0.821–1.498	0.499	1.309	0.816–2.101	0.264	0.985	0.663–1.465	0.942
Hb	0.862	0.593–1.252	0.435	0.913	0.545–1.530	0.729	0.800	0.456–1.404	0.437
Platelet	1.007	0.999–1.015	0.077	1.011	0.999–1.023	0.061	1.001	0.990–1.013	0.818
Peripheral arthritis	0.213	0.451–35.508	0.213	1.500	0.134–16.819	0.742	—	—	—
Enthesitis	2.737	0.744–10.074	0.130	1.800	0.345–9.399	0.486	5.444	0.537–55.203	0.152
Uveitis	0.970	0.082–11.508	0.981	—	—	—	1.0	0.077–13.016	1.0

OR = odds ratio; CI = confidence interval; BMI = body mass index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; NSAID = non-steroidal anti-inflammatory drugs; DMARD = disease-modifying anti-rheumatic drugs; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; WBC = white blood cell; Hb = hemoglobin; probability value < 0.05

Table 4: Multivariate logistic regression analysis of predictors of response to anti-TNF drugs to all patients

	OR	95% CI	*P*-value
BASDAI baseline	22.765	0.634–817.661	0.087
BASFI baseline	1.723	0.374–7.927	0.485
ESR, mm/h	0.864	0.374–1.046	0.134
CRP, mg/L	1.502	1.038–2.175	**0.031**

OR= odds ratio; CI = confidence interval; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; probability value < 0.05

Table 5: ROC analysis of predictors of response to anti-TNF drugs after 3 months in AS patients

Variables	AUC	*P*-value	Cut point	Sensitivity	Specificity
CRP, mg/L	0.965	<0.001	>7.5	94.29%	88.24%
ESR, mm/h	0.824	<0.001	>32	74.29%	94.12%

ROC = receiver operating characteristics; TNF = tumor necrosis factor; AUC = area under the curve; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; probability value < 0.05

or due to structural damage which does not respond to treatment, so patients in our study might have high baseline BASFI due to higher disease activity not due to structural damage, so that they responded better.

The better response of patients with raised inflammatory markers might identify patients with more active disease who are more likely to benefit from anti-TNF treatment than patients with chronic, less active disease.[6] This was shown in Visvanathan *et al.*'s study,[16] which showed that patients with raised inflammatory markers had more spinal inflammation detected by MRI.

The limitation of the study is the short duration of follow-up. However, this should not affect the results as 2016 Update of the ASAS-EULAR Management Recommendations for axial spondyloarthritis recommended that patients should be evaluated after 12 weeks of starting anti-TNF therapy and if there is no response, he/she should be switched to another anti-TNF or IL-17 inhibitor.[13]

Conclusions

1. Raised inflammatory markers (CRP and ESR) at baseline predict better response to anti-TNF drugs in AS patients.
2. CRP had better prediction of response to anti-TNF drugs than ESR.

Recommendations

1. Inflammatory markers can be checked before starting anti-TNF in AS patients, especially CRP to predict patients with good response to the treatment.
2. A study with longer duration and larger sample size is recommended to confirm the results of this study.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379-90.
2. Khan MA. A worldwide overview: The epidemiology of HLA-B27 and associated spondyloarthritides. In: Calin A, Taurog JD, editors. The Spondyloarthritides. Oxford, UK: Oxford University Press; 1998. pp. 17-26.
3. Lee W, Reveille JD, Weisman MH. Women with ankylosing spondylitis: A review. Arthritis Rheum 2008;59:449-54.
4. Khan MA. Clinical features of ankylosing spondylitis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. Philadelphia: Elsevier Ltd; 2003. pp. 1161-81.
5. Al-Rawi ZS, Al-Shakarchi HA, Hasan F, Thewaini AJ. Ankylosing spondylitis and its association with the histocompatibility antigen HL-A B27: An epidemiological and clinical study. Rheumatol Rehabil 1978;17:72-5.
6. Glintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: Results from 8 years' surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis 2010;69:2002-8.
7. Arends S, Brouwer E, van der Veer E, Groen H, Leijsma MK, Houtman PM, *et al*. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: A prospective longitudinal observational cohort study. Arthritis Res Ther 2011;13:94.
8. Lord PA, Farragher TM, Lunt M, Watson KD, Symmons DP, Hyrich KL; BSR Biologics Register. Predictors of response to anti-TNF therapy in ankylosing spondylitis: Results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2010;49:563-70.
9. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis 2004;63:665-70.
10. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York Criteria. Arthritis Rheum 1984;27:361-8.
11. Rudwaleit M. New classification criteria for spondyloarthritis. Int J Adv Rheumatol 2010;8:1-7.
12. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, *et al*. The Assessment of Spondyloarthritis International Society (ASAS) handbook: A guide to assess spondyloarthritis. Ann Reum Dis 2009;68:1-44.
13. Van der Heijde D, Ramiro S, Landewé R, *et al*. 2016 Update of the ASAS-EULAR Management Recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978-91.
14. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, *et al*. A new approach to defining functional ability in ankylosing spondylitis: The development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
15. Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis 2008;67:1276-81.
16. Visvanathan S, Wagner C, Marini JC, Baker D, Gathany T, Han J, *et al*. Inflammatory biomarkers, disease activity and spinal disease measures in patients with ankylosing spondylitis after treatment with infliximab. Ann Rheum Dis 2008;67:511-7.