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**RESEARCH PAPER**

## **The impact of understanding the difference in response of TNF $\alpha$ and CXCL13 in patients with rheumatoid arthritis and ankylosing spondylitis concerning treatment strategy of both diseases**

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### **Abstract**

**Introduction:** Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic inflammatory conditions that damage joints and impair patient's physical fitness. Despite sharing many drugs in their treatment guidelines, they have many differences in their pathogenicity. It is generally understood that a mismatch between pro- and anti-inflammatory cytokine activity promotes autoimmune and chronic inflammation. However, it is still unclear how cytokines are arranged within such complex signaling pathways, and hence which cytokine would be the better target for the evolution of treatments.

**Methods:** This cross-sectional study included 71 patients, 45 with RA, and 26 with AS. According to the type of the treatments, RA patients were divided into three groups (1,2,3), and AS patients were divided into 2 groups (4,5) Data collection was made by clinical examination and specially designed questionnaire form. Five to seven milliliters of blood were collected, centrifuged and the serum was stored at -24 C till the time of assay. Serum TNF $\alpha$ , CXCL13, and ICAM1 were determined by the ELISA. CRP is measured by the photometric method, and ESR by the Wintrobe method. Data were analyzed statistically utilizing the SPSS program (version 26).

**Results:** Eighty-two percent of patients with RA were females, and (18%) were males, their mean age was (51.84  $\pm$  10.74) years and their mean weight was (73.28  $\pm$  13.17) Kg. Regarding AS, (4%) of the patients were females and (96%) were males, with a mean age was (41.88  $\pm$  10.95) years and mean weight was (78.67  $\pm$  13.4) Kg. Serum inflammatory parameters except ICAM1 were significantly higher in patients with RA than in those with AS, regardless of the treatment type.

**Conclusion:** TNF $\alpha$  is significantly correlated with DAS-CRP, ASDAS in patients with RA and AS but its level is significantly higher in patients with RA. Serum CXCL13 correlates with disease activity in patients with RA and could be used as a target for the evolution of new treatments while it has a minor role in patients with AS.

**Key words:** Rheumatoid arthritis, ankylosing spondylitis, etanercept, TNF alpha, ICAM, CXCL13

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### **Introduction**

Both rheumatoid arthritis and ankylosing spondylitis are chronic progressive diseases that affect patient quality of life and have a socioeconomic burden on both the patient himself and the health care system.<sup>1</sup> Patients with

rheumatoid arthritis and ankylosing spondylitis can get benefits from monitoring serum chemokines which can predict the disease activity and treatment efficacy.<sup>2</sup> Furthermore, the role of inflammatory chemokines is different between the two diseases as some of them have a crucial effect in the pathogenesis of both diseases like tumor necrosis factor alpha (TNFa), while other chemokines such as Chemokine (C-X-C motif) ligand 13 (CXCL13) have a major role in rheumatoid arthritis with a negligible role in ankylosing spondylitis;<sup>3-5</sup> this certainly yields more rational and effective treatment strategies of certain anti-chemokine drugs which are specific for one disease more than the other disease.<sup>6,7</sup> On the other hand, gene polymorphisms can predict DMARDs and anti-TNF medication response in autoimmune diseases, hence new markers or utilization of already described biomarkers are essential in both rheumatoid arthritis and ankylosing spondylitis. Monitoring patients who received anti-TNF therapy (such as etanercept or infliximab), may help physicians to modify treatment and avoid unwanted toxicity as a result of improved knowledge of interpersonal variation.<sup>8-11</sup> The financial burden of the anti-rheumatic drugs in general and the biological therapy specifically necessitates the need to determine the suitable type of single treatment or combination of treatment modalities. In addition, the best frequency, and duration of therapy, and whether the medication is equally successful in patients with controlled disease as well as those with uncontrolled disease, also require to be investigated.<sup>12</sup> The present study, therefore, aimed at finding a specific chemokine that has a major role in RA and AS disease processes; this may help in chemokine specific targeted therapy.

## Patients & Methods

### *Study population and patient selection*

The sample size was carefully calculated. Seventy-one patients with rheumatoid arthritis or ankylosing spondylitis were recruited for the study. These patients were diagnosed by their care providers and were scheduled to receive methotrexate or etanercept or their combination as described in (Table-1). Sampling errors can be minimized by accurate planning and comprehension of the sampling technique. A simple random sampling was used by randomly selecting individuals for the cases in each group. Patients were selected from Basrah Teaching Hospital, Basrah Specialized Biological Drugs Clinic, and patient's rheumatology Clinic.

### *Ethical Approval*

The study was approved by Basrah Health Directorate and the Scientific Research Ethical Committee at Basrah College of Medicine. The research strategy was described to the patients, emphasizing that the study outcome is directed toward a significant benefit to the patients. All patients were ready to participate in the trial and expressed their verbal and written informed consents.

### *Study design*

The study was a cross-sectional investigation, during the period from December 2020 to December 2021. Seventy-one (71) patients were recruited for the study. Two types of diseases were chosen; rheumatoid arthritis and ankylosing spondylitis. Forty-five (45) patients were allocated for rheumatoid arthritis group and (26) patient was allocated for ankylosing spondylitis group.

**Table 1.** Study design

Rheumatoid arthritis patients				
Groups	No. of patients	Treatment	Dose	Mean duration of treatment (months), Mean $\pm$ SD
Group 1	13	Etanercept	50 mg weekly	29.5 $\pm$ 25.4
Group 2	17	Methotrexate	12.5-37.5 mg weekly	18 $\pm$ 12.85
Group 3	15	Methotrexate and etanercept	(12.5-37.5 mg MTX) +(50 mg etanercept) weekly	35.8 $\pm$ 62.6
Ankylosing spondylitis patients				
Groups	No. of patients	Treatment	Dose	Mean duration of treatment (months), Mean $\pm$ SD
Group 4	5	Etanercept and methotrexate	(12.5-37.5 mg MTX) + (50 mg etanercept) weekly	44 $\pm$ 70.6
Group 5	21	Etanercept	50 mg weekly	21.9 $\pm$ 23.4

### ***Inclusion Criteria***

1. Patients who were diagnosed as RA or AS.
2. Adults above 1348 years.
3. Patients in clinical remission or active disease.
4. Scheduled for etanercept maintenance treatment, regardless of interval / dosing regarding RA and AS on biological treatment.

### ***Exclusion Criteria***

Patients with severe heart, liver, or renal failure.

### ***Clinical evaluation***

Each participant underwent full clinical evaluation including; patients' interview, proper history taking about duration of disease, frequency and severity of symptoms, drug history, comorbidities, socio-economic status, and weight measurement. Examination of the hands, elbows, shoulders, knees and ankles for tenderness and swelling was made regarding RA patients, and spine and hip examination in case of AS patients. Finally, disease activity score of 28 joints for RA (DAS-CRP)<sup>13</sup> and ankylosing spondylitis disease activity score (ASDAS)<sup>14</sup> was calculated for both diseases.

### ***Measurement of the inflammatory markers***

Five to seven millilitres of blood were taken from antecubital veins, placed in a disposable plain

tube, and left at room temperature for 30 minutes. The samples were then centrifuged at 1000 RPM for 20 minutes to separate the serum. The serum was placed in a new tube and stored in a deep freezer at - 24°C until the time of analysis. Part of the serum was used for estimation of TNF $\alpha$  and CXCL13. The level of serum TNF $\alpha$ , CXCL13, and ICAM1 were determined by ELISA method using Human specific kits for microplate reader device (MyBio Source company, USA), and following the manufacturer instructions. CRP was measured by COBAS INTEGRA 400 plus analyser depending on photometric method (Roche Company, Switzerland). ESR was measured by ESR measurement rack according to Wintrobe method.

### ***Statistical analysis***

Statistical calculations were done using Statistical Package for the Social Sciences version 26 (SPSS Inc.). The differences between groups were analysed by non-parametric Mann-Whitney test for dichotomous variables and Kruskal–Wallis H test for polychotomous variables in abnormally distributed data. An independent t-test regarding the dichotomous variables and a one-way ANOVA test regarding polychotomous variables in normally distributed data. P-values of < 0.05 were considered statistically significant.

## **Results**

### ***Demographical characteristics***

A total of 71 patients were enrolled in the study, 45 patients with rheumatoid arthritis (RA) and 26 were with ankylosing spondylitis (AS). Regarding RA, there were 37 females (82.2%) and 8 males (8%), with a mean age of 51.84  $\pm$  10.74 and a mean body weight of 73.28  $\pm$  13.17.

Other patient characteristics are listed in the table (2). Regarding AS, there was one female (3.8%) and 25 males (96.2%). Their mean age was  $41.88 \pm 10.95$  and their mean body weight was  $78.67 \pm 13.4$ . Other patient characteristics are listed in the table (2).

**Table 2.** Demographical characteristics.

Variables		Rheumatoid arthritis		Ankylosing spondylitis	
		No.	(%)	No.	(%)
Age (years) (mean ± SD)		51.84 ± 10.74		41.88 ± 10.95	
Weight (Kg) (mean ± SD)		73.28 ± 13.17		78.67 ± 13.4	
Gender	Male	8	17.8	25	96.2
	Female	37	82.2	1	3.8
Education	Illiterate	18	40.0	2	7.7
	Primary education	10	22.2	9	34.6
	Intermediate education	6	13.6	7	26.9
	Secondary education	1	2.2	1	3.8
Occupation	Higher education	6	13.3	7	26.9
	Non-employee	39	86.7	13	50
	Employee	6	13.3	12	46.2
Marital status	Retired	0	0	1	3.8
	married	42	93.3	22	84.6
	single	2	4.4	2	7.7
	Widow/divorced	1	2.2	2	7.7

**Effect of (MTX+ETN) on inflammatory parameters in patients with RA and AS (mean ± SD).**

In patients with RA treated with (MTX+ETN), serum levels of TNFa ( $77.66 \pm 26.76$ ), CXCL13 ( $220.88 \pm 132.11$ ), CRP ( $17.18 \pm 7.33$ ), and ESR ( $32.67 \pm 16.96$ ) levels were significantly higher than the respective levels of TNFa ( $48.55 \pm 20.69$ ), CXCL13 ( $71.27 \pm 28.45$ ), CRP ( $10.0 \pm 1.87$ ), ESR ( $13.20 \pm 10.40$ ) in patients with AS for the same type and dose of treatment, while serum ICAM1 showed no significant difference. (Table-3).

**Table 3.** Effect of (MTX+ETN) on inflammatory parameters in patients with RA and AS

Groups	Disease (n)	Parameters (mean ± SD)				
		TNF (pg/ml)	CXCL13 (pg/ml)	ICAM 1 (ng/ml)	CRP (mg/l)	ESR (mm/h ou)
Group 3 (MTX+ETN)	RA (15)	$77.66 \pm 26.76$	$220.88 \pm 132.11$	$148.71 \pm 52.91$	$17.18 \pm 7.33$	$32.67 \pm 16.96$
Group 4 (MTX+ETN)	AS (5)	$48.55 \pm 20.69$	$71.27 \pm 28.45$	$161.0 \pm 20.65$	$10.0 \pm 1.87$	$13.20 \pm 10.40$
	P-value	0.041	0.024	0.624	0.047	0.032

An independent T-test was used to compare the mean of inflammatory parameters.

**Effect of etanercept on inflammatory parameters in patients with rheumatoid arthritis and ankylosing spondylitis**

Similar to treatment with the combination, patients with RA treated with (ETN) alone, serum levels of TNFa ( $76.47 \pm 25.83$ ), CXCL13 ( $246.16 \pm 152.82$ ), CRP ( $20.8 \pm 9.35$ ), ESR ( $37.0 \pm 22.19$ ) levels were higher than the respective levels of TNFa ( $45.51 \pm 35.94$ ), CXCL13 ( $83.94 \pm 44.09$ ), CRP ( $11.11 \pm 9.93$ ) and ESR ( $18.19 \pm 17.94$ ) in patients with AS. Again, serum ICAM1 showed no significant difference. (Table-4).

**Table 4.** Effect of etanercept on inflammatory parameters in patients with rheumatoid arthritis and ankylosing spondylitis

Groups	Disease	Parameters (mean ± SD)				
		TNF (pg/ml)	CXCL13 (pg/ml)	ICAM 1 (ng/ml)	CRP (mg/l)	ESR (mm/hour)
Group 1 (ETN)	RA (13)	$76.47 \pm 25.83$	$246.16 \pm 152.82$	$203.78 \pm 110.19$	$20.8 \pm 9.35$	$37.0 \pm 22.19$
Group 5 (ETN)	AS (21)	$45.51 \pm 35.94$	$83.94 \pm 44.09$	$172.81 \pm 69.73$	$11.11 \pm 9.93$	$18.188 \pm 17.94$
	P-value	0.011	0.001	0.321	0.08	0.03

An independent T-test was used to compare the mean of inflammatory parameters.

### Correlation between TNFa, CXCL13, and DAS28-CRP or ASDAS

There was a significant correlation between serum TNFa levels and disease activity score (DAS-CRP or ASDAS) in patients with RA and patients with AS. There was a significant

correlation between serum CXCL13 and DAS-CRP in patients with RA while such correlation was lacking between serum CXCL13 and ASDAS in patients with AS. (Figure-1).

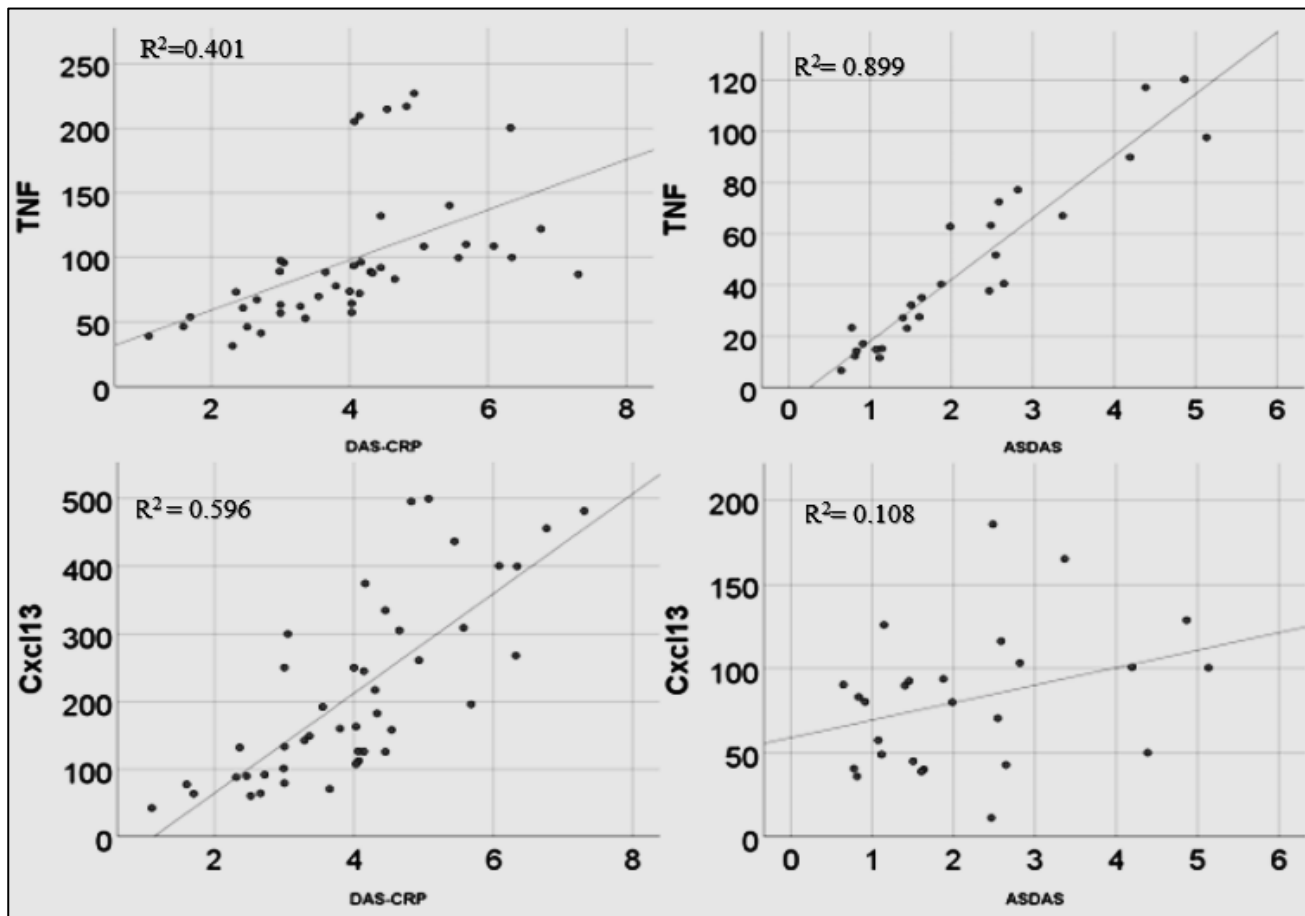


Fig 1. Correlation between serum CXCL13, TNFa levels in patients with RA and AS with their disease activity scores.

DAS-CRP: disease activity score in 28 joints for patients with RA. ASDAS: disease activity score for AS patients.

### Discussion

There are several previous studies that evaluated the role of treatments that are targeting inflammatory cytokines like TNF in patients with

RA or AS individually. However, there were little information about the differences in behaviour of these cytokines in both diseases that may affect

the response to drugs as well as optimization of the dose for each disease. The purpose of this study was to evaluate the response of each of these inflammatory cytokines (TNFa and CXCL13) to each group of treatment aiming to concentrate on the best method and drug to target the specific cytokine that have a major role in the disease pathogenesis. It is well known that serum level and synovial fluid level of TNFa in patients with RA is higher than that of patients with AS, despite that a fixed dose of ETN is used for both diseases.<sup>15-17</sup> Our study found that there was no significant difference in serum TNFa level between patients treated with ETN or those who were treated with ETN+MTX in patients with RA or AS. Furthermore, the present study found that serum TNFa level in patients with RA is higher than that of AS. This may be attributed to the reduction of serum TNF-R1 level in patients with AS on ETN treatment containing protocols while this observation does not occur in patients with RA, in consistent with the assumption that soluble TNF-R1 levels are linked to TNF-function and its inflammatory reactions.<sup>18-20</sup> The fact that TNF-blockers don't affects TNF-R1 levels in RA patients could be interpreted by different regulators of TNF-signalling in AS patients compared to RA patients.<sup>15</sup> A systematic review of CXCL13 as a biomarker of disease and treatment response in RA was published in November 2020 and highlighted the crucial role of CXCL13 in RA, which concluded that there is a heterogeneity in the published studied about the use of CXCL13 as routine biomarker for monitoring the response to treatment.<sup>4</sup> CXCL13 levels were found to be lower in response to biologics such as anti-TNF, anti-IL6, B cell depletion, and small molecule JAK inhibitors in the studies. The decrease in CXCL13 was only detected in treatment responders while the non-responders show no reduction in serum CXCL13

level in some studies.<sup>21</sup> Evidence is also contradictory as a predictor of therapeutic efficacy, CXCL13 levels linked disease remission failure in individuals on biological DMARDs, especially when paired with positive autoantibodies.<sup>22</sup> There is very limited data about the role of CXCL13 in AS. This study found that the level of CXCL13 in patients with RA is significantly higher than its level in patients with AS regardless the treatment type; this may be explained by the fundamental role of CXCL13 in RA pathogenesis and progression while it may have a negligible role in AS pathogenesis. In our study, patients with uncontrolled RA and relatively reduced level of TNFa tend to have high CXCL13 despite the sufficient period of ETN therapy; this could reflect that an alternate pathway mediates CXCL13 activity, or that there is an 'escape' mechanism, independent of TNF, has emerged in cases where the response didn't occur. In this state, development of a drug which is targeting CXCL13 or its receptor (CXCR5) may be beneficial. Klimatcheva et al.,<sup>7</sup> in 2015 evaluated the role of CXCL13 antibody for the treatment of autoimmune disorders, they described the development and functionality testing of MAb 5261, a novel anti-human CXCL13 antibody, as well as its pharmacological properties. The antibody interacts to CXCL13 in humans. It effectively and precisely blocks CXCL13-induced chemotaxis in human and murine B cells, and also CXCR5 receptors endocytosis mediated by CXCL13. In this study, serum level of ICAM1 was significantly associated with disease activity scores in both RA and AS without significant differences between the two diseases. Dustin and his colleagues<sup>23</sup> analysed the production and expression of ICAM-1 in the tissue and discovered that inflammatory and dendritic cells in germinal centres and T-cell regions in lymphoid organs

expressed the protein at high levels. These cells are thought to be crucial in immunological and inflammatory processes and depend on the strength of the inflammation rather than the type of the disease. The present study found that serum CRP level and ESR are significantly higher in RA patients than AS patients. It is well known from previous studies that mean CRP and ESR values are higher in patients with RA than patients with AS, furthermore, these markers usually elevated in 40% to 50% from AS only<sup>24-25</sup> This finding could be explained by the fact that the values of these parameters are correlated with the degree of peripheral involvement which is prominent in RA rather than the axial distribution of AS. This study has several limitations, firstly Basrah has single rheumatological center and single biological clinic which receive patients two days a week. This may limit reach for patients. Secondly, as patients are taken from a single centre, and a single observer was responsible for patient's recruitment, bias cannot be completely avoided. In conclusion, CXCL13 is a novel biomarker for monitoring treatment in patient with RA. However, some patients with RA who were not responding to treatment have elevated CXCL13 levels. This may highlight the need for new treatments which targets CXCL13 or its receptor. On the other hand, this study concludes that CXCL13 has a negligible role in AS. TNF $\alpha$  has essential role in both RA and AS and can be used to predict treatment in both diseases.

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### References

1. Katchamart W, Narongroeknawin P, Chanapai W, Thaweeratthakul P. Health-

- related quality of life in patients with rheumatoid arthritis. *BMC Rheumatology*. 2019; 3(1): 34.
2. Li Y, Yuan L, Yang J, Lei Y, Zhang H, Xia L, et al. Changes in serum cytokines may predict therapeutic efficacy of tofacitinib in rheumatoid arthritis. *Mediators of Inflammation*. 2019; 2019:Article ID 3013716, 8 pages.
3. Kazanietz MG, Durando M, Cooke MJ. CXCL13 and its receptor CXCR5 in cancer: inflammation, immune response, and beyond. *Frontiers in Endocrinology*. 2019; 10:471.
4. Bechman K, Dalrymple A, Southey-Bassols C, Cope AP, Galloway JBJ. A systematic review of CXCL13 as a biomarker of disease and treatment response in rheumatoid arthritis. *BMC Rheumatology*. 2020; 4(1):1-9.
5. Jang D-i, Lee A, Shin H-Y, Song H-R, Park J-H, Kang T-B, et al. The role of tumor necrosis factor alpha (TNF- $\alpha$ ) in autoimmune disease and current TNF- $\alpha$  inhibitors in therapeutics. *International Journal of Molecular Sciences*. 2021; 22(5): 2719.
6. Ridgley LA, Anderson AE, Pratt AG. What are the dominant cytokines in early rheumatoid arthritis? *Current Opinion in Rheumatology*. 2018; 30(2): 207.
7. Klimatcheva E, Pandina T, Reilly C, Torno S, Bussler H, Scrivens M, et al. CXCL13 antibody for the treatment of autoimmune disorders. *BMC Immunology*. 2015; 16(1):1-17.
8. Prieto-Perez R, Cabaleiro T, Dauden E, Abad-Santos FJ. Gene polymorphisms that can predict response to anti-TNF therapy in patients with psoriasis and related autoimmune diseases. *the*

- pharmacogenomics journal. 2013; 13(4): 297-305.
9. Netz U, Carter JV, Eichenberger MR, Dryden GW, Pan J, Rai SN, et al. Genetic polymorphisms predict response to anti-tumor necrosis factor treatment in Crohn's disease. *World Journal of Gastroenterology*. 2017; 23(27): 4958.
  10. Mikhaylenko DS, Nemtsova MV, Bure IV, Kuznetsova EB, Alekseeva EA, Tarasov VV, et al. Genetic polymorphisms associated with rheumatoid arthritis development and antirheumatic therapy response. *International Journal of Molecular Sciences*. 2020; 21(14): 4911.
  11. Daekh NAK, Mohammed KA, Ali NH. Polymorphism of HLA-B27 among Ankylosing Spondylitis Patients in Basrah, Iraq. *Scientific Journal of Medical Research*. 2020; 4(13): 12-16
  12. Reveille JD, Ximenes A, Ward MM, Deodhar A, Clegg DJ. Economic considerations of the treatment of ankylosing spondylitis. *The American Journal of the Medical Sciences*. 2012; 343(5): 371-374.
  13. Greenmyer JR, Stacy JM, Sahnoun AE, Beal JR, Diri EJAOR. DAS28-CRP cutoffs for high disease activity and remission are lower than DAS28-ESR in rheumatoid arthritis. *American College of Rheumatology*. 2020; 2(9): 507-511.
  14. Jun JB, Koo BS, Lee S, Kim J, Kang J, Kim TH. ASDAS Is More Important Than BASDAI in Advanced Ankylosing Spondylitis. In 2019 ACR/ARP Annual Meeting 2019 Nov 10. WILEY.
  15. Schulz M, Dotzlaw H, Neeck GJBri. Ankylosing spondylitis and rheumatoid arthritis: Serum levels of TNF-and its soluble receptors during the course of therapy with etanercept and infliximab. *BioMed Research International* 2014; 2014: 675108.
  16. Edrees A, Misra S, Abdou NJC, rheumatology e. Anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis: correlation of TNF-alpha serum level with clinical response and benefit from changing dose or frequency of infliximab infusions. *clinical and experimental rheumatology*. 2005; 23(4): 469.
  17. San Koo B, Jo S, Kwon E, Shin JH, Hur J-W, Kim T-H. Effect of biologics in the level of cytokines in the synovial fluid of patients with ankylosing spondylitis. *Korean Journal of Internal Medicine*. 2020; 35(2): 465.
  18. Scalzo P, Kümmer A, Cardoso F, Teixeira ALJ. Increased serum levels of soluble tumor necrosis factor- $\alpha$  receptor-1 in patients with Parkinson's disease. *Journal of Neuroimmunology*. 2009; 216(1-2): 122-125.
  19. Matthey DL, Glossop JR, Nixon NB, Dawes PTJA, Rheumatology ROJotACo. Circulating levels of tumor necrosis factor receptors are highly predictive of mortality in patients with rheumatoid arthritis. *Arthritis & Rheumatology*. 2007; 56(12): 3940-3948.
  20. Coelho FM, Reis HJ, Nicolato R, Romano-Silva MA, Teixeira MM, Bauer ME, et al. Increased serum levels of inflammatory markers in chronic institutionalized patients with schizophrenia. *Neuroimmunomodulation*. 2008; 15(2): 140-144.
  21. Bugatti S, Manzo A, Vitolo B, Benaglio F, Binda E, Scarabelli M, et al. THU0546 Serum CXCL13 as a biomarker of disease activity and severity in IN rheumatoid arthritis. Comparison with acute phase



- reactants and the autoantibody profile. *Med of Inflamm.* 2014; 73(2): 371.
22. Bugatti S, Manzo A, Vitolo B, Benaglio F, Caporali R, Montecucco C. SAT0087 Serum Levels of CXCL13 Refine The Predictive Ability of Autoantibodies To Identify Unstable Remission in Early Rheumatoid Arthritis. *Annals of the Rheumatic Diseases* 2016; 75(2): 696.
  23. Dustin ML, Rothlein R, Bhan AK, Dinarello CA, Springer TAJTJoI. Induction by IL 1 and interferon-gamma: tissue distribution, biochemistry, and function of a natural adherence molecule (ICAM-1). *The Journal of Immunology.* 1986; 137(1): 245-254.
  24. Illahi MI, Amjad S, Alam SM, Ahmed ST, Fatima M, Shahid MAJC. Serum Tumor Necrosis Factor-Alpha as a Competent Biomarker for Evaluation of Disease Activity in Early Rheumatoid Arthritis. *Cureus Journal of Medical Science.* 2021; 13(5): 314-319
  25. de Vries MK, van Eijk IC, van der Horst-bruinsma IE, Peters MJ, Nurmohamed MT, Dijkmans BA, et al. Erythrocyte sedimentation rate, C-reactive protein level, and serum amyloid A protein for patient selection and monitoring of anti-tumor necrosis factor treatment in ankylosing spondylitis. *Arthritis Care & Research.* 2009; 61(11):1484-1490.

تأثير فهم الاختلاف في أستجابة TNF $\alpha$  و CXCL13 في المرضى الذين يعانون من التهاب المفاصل الرثوي و التهاب الفقرات التصلبي

فيما يتعلق بأستراتيجية العلاج المرضى

**المقدمة:** التهاب المفاصل الرثوي (RA) و التهاب الفقرات للتصلبي (AS) هي حالات التهابية مزمنة تتلف المفاصل وتضعف اللياقة البدنية للمريض. على الرغم من وجود العديد من الأدوية في إرشادات العلاج الخاصة بهم، إلا أن هناك العديد من الاختلافات في طبيعة المرضى. من المفهوم بشكل عام أن عدم التطابق بين نشاط (السايتوكين) المحفز والمضاد للالتهابات يعزز المناعة الذاتية والالتهابات المزمنة. ومع ذلك، لا يزال من غير الواضح كيف يتم ترتيب السيتوكينات ضمن مسارات الإشارات المعقدة، وبالتالي ما هو السيتوكين الذي سيكون الهدف الأفضل لتطور العلاجات.

**الطريقة:** تضمنت هذه الدراسة المقطعية 71 مريضاً، 45 مصاباً بالتهاب المفاصل الرثوي، و 26 مريضاً مصاباً ب التهاب الفقرات للتصلبي. وفقاً لنوع العلاج، تم تقسيم مرضى التهاب المفاصل الرثوي إلى ثلاث مجموعات (1،2،3)، وتم تقسيم مرضى التهاب الفقرات للتصلبي إلى مجموعتين (4،5). تم جمع البيانات عن طريق الفحص السريري واستمارة استبيان مصممة خصيصاً. تم جمع خمسة إلى سبعة مليلتر من الدم وطردتها مركزياً وتم تخزين المصل عند -24 درجة مئوية حتى وقت الفحص. تم تحديد مصل TNF $\alpha$  و CXCL13 و ICAM1 بواسطة ELISA بينما تم قياس CRP بطريقة القياس الضوئي، و ESR بطريقة Wintrobe تم تحليل البيانات إحصائياً باستخدام برنامج SPSS الإصدار 26.

**النتائج:** اثنان وثمانون في المائة من مرضى التهاب المفاصل الرثوي كانوا من الإناث، و (18٪) من الذكور، وكان متوسط أعمارهم (51،84 - 10،74) سنة ومتوسط وزنهم (73،28 - 13،17) كغم. فيما يتعلق ب التهاب الفقرات للتصلبي 4٪ من المرضى كانوا من الإناث و (96٪) من الذكور بمتوسط عمر (1،88 - 10،95) سنة ومتوسط وزن (78،67 + 13،4) كغم. كانت العلامات الالتهابية في المصل باستثناء ICAM1 أعلى بشكل ملحوظ في المرضى الذين يعانون من التهاب المفاصل الرثوي مقارنة بالمصابين ب التهاب الفقرات للتصلبي، بغض النظر عن نوع العلاج.

**الخلاصة:** يرتبط TNF $\alpha$  ارتباطاً وثيقاً ب DAS-CRP و ASDAS في مرضى التهاب المفاصل الرثوي و التهاب الفقرات للتصلبي لكن مستواه أعلى بشكل ملحوظ في مرضى التهاب المفاصل الرثوي. يرتبط مصل CXCL13 بنشاط المرض لدى مرضى التهاب المفاصل الرثوي ويمكن استخدامه كهدف لتطور علاجات جديدة بينما يكون له دور ثانوي في مرضى التهاب الفقرات للتصلبي

**الكلمات المفتاحية:** التهاب المفاصل الروماتويدي، التهاب الفقار اللاصق، etanercept، TNF alpha، ICAM، CXCL13