Relationship Between Trough Levels of Anti-Infliximab and Serum Biomarkers in Patients With Rheumatoid Arthritis

Sura Mohammed Lateef[1], Ahmed Abdul-Hassan Abbas[1], Mohammed Hadi Alosami[2]

[1] *Department of Microbiology, Al-Nahreen University, Collage of Medicine, Baghdad, Iraq*

[2] *Department of Rheumatology, Baghdad University, Collage of Medicine, Baghdad, Iraq*

Received: 03 Oct. 2024; Accepted: 16 Nov. 2024

Abstract- Rheumatoid arthritis is a chronic condition, characterized by the expression of antibody against self-antigens. Inflammatory cell of synovial tissues secreted numerous cytokines, include tumor necrosis factor alpha. Infliximab was designed to treat several autoimmune diseases. However, a considerable number of patients fail to respond appropriately. To investigate the relationship between trough infliximab serum levels and infliximab antibody with C-reactive protein (CRP), Rheumatoid factor (RF), and Anticyclic citrullinated peptide (ACCP) status. This study examined 83 rheumatoid arthritis patients on infliximab for 6 months duration. Sampling was collected in Rheumatology Unit at (Baghdad Teaching Hospital) from September 2021 to April 2022. Each patient had 3 mL of blood drawn. before the next dosage of medication. Anti-infliximab antibody, trough infliximab, and ACCP levels were measured using ELISA, while RF and CRP status were determined using an agglutination test. Ages of the patients ranged between 30-75 years old, (66 females and 17 males), and 44.6% of patients were smokers. In this study, 41 out of 83 patients were responder for infliximab therapy. The seropositivity of anti-drug antibodies was 50% in non-responder and 48.80% in responder patients. In contrast, the infliximab trough level classification as low and high in responder and non-responder patients was high in 56.1 %, and 40.5% of patients respectively. The difference between the two groups was statistically non-significant *P*=0.114. In addition, 74 patients tested positive for anti-cyclic citrullinated peptide. (89.2%), abnormal CRP levels were found in 54 (65.1%) patients, and seropositivity of Rheumatoid factor was found in 52 (62.7 %) of the patients. There was a negative relationship between smoking and responsiveness to infliximab. (r= -0.295 *P* 0.007) while there was a positive correlation between anti-infliximab antibodies with CRP and RF (*P*=0.026). Likewise, ACCP and serum trough infliximab levels were correlated significantly (*P*=0.014). Antidrug antibody seropositivity correlates positively with CRP and RF status and between ACCP and serum trough infliximab in RA patients while there is a negative correlation between smoking and early response to infliximab.

Acta Med Iran 2024;62(November-December):338-345.

Keywords: Anti cyclic citrullinated protein; C reactive protein; Infliximab; Rheumatoid arthritis; Rheumatoid factor

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by persistent synovitis and the expression of autoantibodies. The exacted mechanism of which is not fully understood (1,2). The major role of pro inflammatory cytokines such (TNF-a) has resulted in the advancement and clinical use of biological factors that inactivate these cytokines. Treatment with infliximab, an anti-TNF alpha monoclonal antibody, frequently results in significant clinical effectiveness, including a delay in radiological development, a drop in blood CRP, and a reduction in the expression of inflammatory cytokines caused by TNF-a. Auto antibodies such as rheumatoid factor RF, and anticyclic citrullinated peptides are often identified in patients prior to the onset of arthritis (3,4).

Corresponding Author: S.M. Lateef
Department of Microbiology, Al-Nahreen University, Collage of Medicine, Baghdad, Iraq
Tel: +9647708438233, E-mail address: sura.sura417@gmail.com

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by the immune system's attack on joint tissues, leading to pain, swelling, and eventual joint damage. In Iraq, the prevalence of RA presents significant public health concerns, necessitating a deeper understanding of its underlying mechanisms and potential biomarkers for effective management. Recent studies have indicated that serum biomarkers may play a crucial role in assessing disease activity and treatment response in RA patients. This article focuses on the association between trough levels of anti-infliximab—a monoclonal antibody used in the treatment of RA—and various serum biomarkers among Iraqi patients (5-8).

By examining these relationships, the study aims to elucidate the mechanisms by which anti-infliximab influences disease progression and response to therapy, thereby contributing valuable insights into personalized treatment approaches for RA. The findings could enhance our understanding of how specific biomarkers correlate with treatment efficacy, ultimately improving patient outcomes in this challenging autoimmune condition (5-8).

The identification of autoantibodies such as RF and ACCP has given a great foundation for early diagnosis and disease progression. Rheumatoid factor is a commonly used serum biomarker for the diagnosis of RA and ACCP was highly correlated with early RA (9).

C-reactive protein (CRP) one of the best indicators of inflammation. The CRP reflects short-term changes in disease activity in RA. TNF is a prominent cytokine with various biological functions in RA. In individuals who do not respond to traditional synthetic disease-modifying antirheumatic drugs, blocking TNF with antibodies has become the standard of care. The mechanisms behind tolerance break against citrullinated proteins and the generation of ACPAs are yet unknown, however environmental contaminants such as smoking have been postulated to have a role (10). The positivity for anti-CCP antibodies or RF is a predictive response to Infliximab. A correlation between RF and ACCP with clinical disease activity has been reported. In Iraq, few data are available on the relationship between trough level and anti-infliximab with serum biomarkers as indicators for response to infliximab treatment, so this study was conducted.

Materials and Methods

Patients and methods

This research was carried out from September 2021 to April 2022. Blood samples were collected from 83 individuals with rheumatoid arthritis who were receiving infliximab infusion therapy in Baghdad Teaching Hospital's Rheumatology unit. RA patients were divided into two groups (41 responders and 42 non-responders) following six months of treatment with TNF-inhibitor infliximab on a conventional regimen (3 mg/kg) for two weeks, six weeks, and thereafter every six weeks. Before the next dosage of medication, 3 ml of blood was taken from each patient in a gel tube and kept at room temperature for 30 minutes before centrifugation at 3000 rpm for five minutes, all sera were collected and kept at -20°C until use. ELISA was used to determine trough infliximab concentration, anti-infliximab antibody levels, and ACCP, while an agglutination test was used to determine RF and CRP status.

Clinical disease activity for each RA patient was measured before to the next dose of infliximab infusion therapy by simply adding the number of swollen/tender joints. of 28 joints along with patient and physician global evaluation on VAS (0-10) scale for disease activity estimation to categorize patients as responders or non-responders based on remission and low disease activity as a responders However, as non-responders, they have moderate to high disease activity, CDAI is classified into five categories: remission (2.8), low disease activity (2.8-10), moderate disease activity (10-22), and high disease activity (>22). The diagnosis of each case was determined by a clinical examination performed by a rheumatologist and confirmed by a lab test. Direct interviews with patients as well as a questionnaire were used to collect data. Furthermore, the initial CDAI was obtained at the request of the patient and was assessed before to the use of biological therapy.

Inclusion criteria

Patients with rheumatoid arthritis on infliximab 6 months.

Exclusion criteria

Patients with rheumatoid arthritis who also have other autoimmune or chronic disorders.

Statistical analysis

This prospective study's statistical analysis was carried out using the statistical package for social sciences (SPSS) 20.0 and GraphPad.Prism version 7.

Table 1. Serum levels of ACCP, CRP, and RF of rheumatoid arthritis patients

		Mean±SD (range)
ACCP	Positive	74 (89.2%)
	Negative	9 (10.8%)
CRP mg/l	Abnormal level	54 (65.1%)
	Normal level	29 (34.9%)
RF IU/l	Positive	52 (62.7)
	Negative	31 (37.3)

Table 2. Association between ACCP seropositivity and the early response to infliximab

		Response		Total
		Non-responder	Responder	
ACCP	**Positive**	34	40	74
		81%	97.5%	89.2%
	Negative	8	1	9
		19%	2.5%	10.8%
Total		42	41	83
P		0.016		

Table 3. Association between CRP status and the early response to infliximab

		Response		Total
		Non-responder	Responder	
CRP	**Abnormal level**	27	27	54
		64.3%	65.85%	65.1%
	Normal level	15	14	29
		35.7%	34.15%	34.9%
Total		42	41	83
P		0.532		

Table 4. The association between RF status and infliximab early response

		Response		Total
		Non-responder	Responder	
RF	**Positive**	24	28	52
		57.1%	68.3%	62.7%
	Negative	18	13	31
		42.9%	31.7%	37.3%
Total		42	41	83
P		0.205		

Table 5. Association of CRP serum status and duration of treatment

		Duration of treatment (weeks)			Total
		8	14	26	
CRP	**Abnormal Level**	20	18	16	54
		64.5%	60.0%	72.7%	65.1%
	Normal Level	11	12	6	29
		35.5%	40.0%	27.3%	34.9%
Total		31	30	22	83
		100.0%	100.0%	100.0%	100.0%
P			0.634		

Results

A total of 83 RA patients were enrolled in the study, the mean age of RA patients was 49.58 (30-75) years. The females and males ratio was 4:1. Among the patients 37 (44.6%) were smokers. In this study, 41 patients out of 83 were responder for infliximab therapy. There were 74 patients who tested positive for anti-cyclic citrullinated peptide (89.2 %), and 54 (65.1 %) had abnormal CRP levels, and Table-1 shows that 52 (62.7 %) of patients had rheumatoid factor seropositivity.

The seropositivity of ACCP in responder was 97.5%

and in non-responder patients was 81 % and *P*=0.016, as shown in Table 2. On the other hand, the abnormal levels of CRP were present in 65.85 % of responder patients while in non-responder patients were 64.3% as shown in Table 3. In addition, the seropositivity of RF in responder patients was 68.3%, and in non-responder patients was 57.1% as shown in Table 4. The abnormal levels of CRP at 8-, 14-, and 26-week's duration of treatment were in 64.5%, 60.0%, and 72.7% of patients respectively, Table 5.

The seropositivity of anti-drug antibodies is (half) 50% in non-responder patients and 48.80% in responder patients as shown in Table 6. On the other hand, the infliximab trough level classified as low and high in responder and non-responder patients were high in 56.1 %, and 40.5% of patients respective, the difference between the 2 groups was statistically non-significant (*P*=0.114) Table 7.

Table 8 shows that there was no statistically significant difference in responsiveness to biological therapies between smokers and nonsmokers.

On the other hand, there was a correlation between CRP and RF. Likewise, there was a correlation between ACCP and serum trough infliximab with *P*=0.014. In addition, Smoking and infliximab responsiveness had a negative correlation. (r= -0.295 p-value0.007) Table 9. Correlation among anti-infliximab antibodies, infliximab trough, CRP RF, ACCP, DAS, delta CDAI, and Smoking.

Table 6. Anti-drug antibody seropositivity in responders and nonrespondersnti-drug antibody seropositivity in responders and nonresponders

		Response		Total
		Non-responder	Responder	
Anti-drug antibody	**Positive**	21	20	41
		50%	48.80%	49.40%
	Negative	21	21	42
		50%	51.20%	50.60%
Total		42	41	83
P		0.543		

Table 7. Association between drug level and clinical response to infliximab

		Response		***P***
		None	Response	
Infliximab serum Level	**Low**	25	18	0.114
		59.5%	43.9%	
	High	17	23	
		40.5%	56.1%	
Total		42	41	83
		100.0%	100.0%	100.0%

Table 8. Association between smoking and the early response to infliximab

		Response		Total
		Non-responder	Responder	
Smoking	**Yes**	21	16	37
		50%	39%	44.60%
	No	21	25	46
		50%	61%	55.40%
Total		42	41	83
P		0.218		

Table 9. Showed a significant correlation between anti-infliximab antibodies with CRP and RF (*P*=0.026)

		ESR mm/hr	Drug ng/ml	ADA (ng/ml)	TNF	ACCP	CRP	RF	DAS 28	Delta CDAI	Smoking	BMI
ESR mm/hr	**r**	1.000	-.226*	-0.026	-0.115	0.039	-0.168	-0.050	-0.120	-0.198	-0.180	-0.165
	p		0.040	0.816	0.299	0.726	0.129	0.653	0.282	0.073	0.102	0.060
Drug (ng/ml)	**r**	-.226*	1.000	0.128	0.015	.269*	0.106	-0.067	-0.012	0.160	0.089	0.061
	p	0.040		0.247	0.895	0.014	0.339	0.545	0.917	0.148	0.424	0.584
Cont. table 9												
ADA	**r**	-0.026	0.128	1.000	-0.025	-0.162	.245*	.244*	-0.117	-0.054	0.035	0.243*

(ng/ml)	**p**	0.816	0.247		0.822	0.143	0.026	0.026	0.292	0.630	0.753	0.027
TNF	**r**	-0.115	0.015	-0.025	1.000	0.046	0.109	-0.059	-0.091	0.130	0.013	0.080
Conc.	**p**	0.299	0.895	0.822		0.679	0.328	0.596	0.414	0.241	0.904	0.470
ACCP	**r**	0.039	.269*	-0.162	0.046	1.000	-0.014	-0.102	-0.148	0.125	0.001	0.039
	p	0.726	0.014	0.143	0.679		0.902	0.357	0.182	0.258	0.993	0.725
CRP	**r**	-0.168	0.106	.245*	0.109	-0.014	1.000	.218*	-0.091	-0.002	-0.105	0.105
	p	0.129	0.339	0.026	0.328	0.902		0.048	0.412	0.985	0.343	0.336
RF	**r**	-0.050	-0.067	.244*	-0.059	-0.102	.218*	1.000	0.142	-0.040	-0.059	-0.056
	p	0.653	0.545	0.026	0.596	0.357	0.048		0.201	0.721	0.595	0.102
DAS28	**r**	-0.120	-0.012	-0.117	-0.091	-0.148	-0.091	0.142	1.000	-0.168	-0.295**	0.020
	P	0.282	0.917	0.292	0.414	0.182	0.412	0.201		0.128	0.007	0.858
Delta	**r**	-0.198	0.160	-0.054	0.130	0.125	-0.002	-0.040	-0.168	1.000	0.024	0.075
CDAI	**p**	0.073	0.148	0.630	0.241	0.258	0.985	0.721	0.128		0.829	0.501
Smoking	**r**	-0.180	0.089	0.035	0.013	0.001	-0.105	-0.059	-0.295**	0.024	1.000	0.001
	P	0.102	0.424	0.753	0.904	0.993	0.343	0.595	0.007	0.829		0.883
BMI	**r**	-0.165	0.061	0.243*	0.080	0.039	0.105	-0.056	0.020	0.075	0.001	1.000
	p	0.060	0.584	0.027	0.470	0.725	0.336	0.102	0.858	0.501	0.883	

Discussion

In the current study, 44.6 % of patients smoke. A prior Iraqi research conducted by Al-Osami *et al.,* indicated that around one-third of patients did not smoke earlier (11). Smokers have been identified as a key component in the development and severity of RA (12). The Previous epidemiology studies have shown smoking as an important risk factor for RA (13). Klareskog *et al*., demonstrated that smoking causes citrullination in the lungs of those who had the HLA-DRB1 SE., thereby provide a substrate for immune activation that finally causes ACPA-positive RA (14). Källberg *et al*., hypothesized that smoking was responsible for 20-25% of overall RA risk and up to 35% of ACPA-positive RA (15). Furthermore, Maria et colleagues discovered an association between smoking and the development of arthritis (16).

Seror *et al*., found a link between active smoking and the risk of RA. Furthermore, early passive tobacco smoking throughout childhood may be linked to an earlier start of RA (17). Sugiyama et al. discovered that smoking is a risk factor for RA among RF-positive males and heavy smokers. The risk of developing RA was approximal twice as high for smokers than for non-smokers. For female smokers, the risk was approximately one to three times higher than for non-smokers (17). Furthermore, the current study found a negative relationship between smoking and clinical response to infliximab (r= -0.295 *P* 0.007). Söderlin *et al.,* colleagues discovered that smokers had considerably lower response rates to infliximab (18). Another study conducted by Song *et al*., reveals that smoking may have an effect on TNF-inhibitors and reduce clinical responsiveness to these medicines used in RA patients (19). Tobacco use is linked to disease progression, chronic inflammation, an increase in adverse medication responses, and a decrease in therapeutic responsiveness. Cigarette smoking increases pro-inflammatory cytokines such as TNF-a and other inflammatory mediators, making them more resistant to anti-TNF medication. An increase in TNF-a may result in increased intake of TNF- inhibitors and a poor response. Other explanations include changes in the pharmacokinetics of TNF antagonists in smokers, such as problems with absorption or more rapid drug elimination (20).

According to the current study, CRP levels were abnormal in 65.1% of RA patients. Furthermore, the Shrivastava *et al.,* study found abnormal elevated CRP levels in RA patients (21). In contrast, another study found that the majority of RA patients have a high percentage of negative CRP test findings (22). In RA patients, CRP blood levels represent inflammatory activity, and persistent CRP increases are associated with increasing joint deterioration (23). This study identified a positive correlation between CRP and RF in RA patients (r=0.218 and *P* 0.048). Similarly, the Dessie *et al*., investigation discovered elevated CRP levels in RF positive individuals (22).

In RA, RF causes the development of an immune complex at the sites of synovial inflammation, resulting in the activation of complemented and leukocyte infiltration. In addition, contributes to the perpetuation of local inflammatory responses thus increasing inflammatory proteins such as CRP, and the levels of immune complexes roughly correspond to the clinical severity and/or progression of the disease (23).

Furthermore, the current investigation discovered a positive correlation between antidrug antibodies and CRP and RF.(*P*=0.026).

Antibodies to infliximab therapy are produced because of its immunogens. Infliximab is an example of

a chimeric antibody, because there are more immunological foreign epitopes, the immune response is more diversified. This may result in the creation of bigger immune complexes (ICs), and so anti-drug antibodies (ADAs) increase neutralization and ICs accelerate clearance of the therapeutic protein, that is created by immune system phagocytic cells, resulting in the prolonged creation of immune complexes (ICs)and causing an inflammatory response and the production of inflammatory cytokines such as IL6 and TNF alpha, as well as acute phase proteins (24).

The present data demonstrated that the RF was positive in 52 (62.7%) of RA patients, a study by Bobbio-Pallavicini indicating that persistent clinical response to anti-TNF medications is related with a considerable decrease in rheumatoid factor blood level (25). A previous Iraqi study by Albarzinji *et al.,* found that 67.69% of RA patients tested positive for RF (26). In the current study, identified no significant association between RF and responsiveness to infliximab (*P* 0.205). Previous studies found that the presence of RF was related with lower clinical response to TNF blocking (25), while other research revealed no correlation between RF status and infliximab response (27). Furthermore, in RA patients, this study discovered a positive correlation between the rheumatoid factor and antidrug antibody (r=0.244 *P*=0.026). RF positivity was related to ADAs, according to a study (28). However other previous research reported no significant association between RF positivity and ADAs to infliximab therapy in RA patients (29). The role of seropositivity in anti-TNF-a response is ambiguous. Prior studies suggest that the presence of RF is associated with a mild DAS28 reduction after 6 months of therapy and a lower probability of achieving remission of the disease (30). In certain cases, exposure to therapeutic proteins (IFX) may further activate the immune system to create anti-drug antibodies in the presence of non-regulated B cells (31).

Moreover, in the current work, Anti-CCP positivity was found in 89.2 % of RA patients. ACPA is detected years before the onset of RA symptoms and appears to be fairly stable throughout the disease, with no substantial shifts from ACPA negative to positive or inversely (10). Laird *et al.,* discovered an association between HLA DRB1 genes and the presence of ACPA. It has been observed that only patients which shared epitope develop ACPA (32). Smoking may activate the immune system in the lungs, This might result in the formation of specific autoantibody types such as RF and ACPA, and In seropositive people who have not yet developed joint inflammation or in patients with a recent beginning of seropositive RA, germinal center-like formations can arise (10). Ozkaya Eker *et al.,* found that 69% of RA patients tested positive for anti-CCP (33). On the other hand, there was a correlation between ACCP and serum through infliximab with *P*=0.014. This study found that even after RA patients were given anti-TNF alpha drugs (Infliximab), the biomarker ACPA was still present in their blood. Another study discovered that the level of ACPA did not alter substantially following treatment with infliximab (28). Alessandri discovered a significant reduction in serum ACPA level following infliximab therapy (27).

Limitations

The number of patients evaluated is rather small, and there was not enough time to collect more samples because these findings are part of the MSc project, which is time limited. In addition to the unavailability of biological treatments (infliximab) continuously in the biological therapy unit.

In conclusion, this study indicates that while the overall response rate to infliximab therapy in rheumatoid arthritis patients was 49.4%, the presence of anti-drug antibodies did not significantly differentiate responders from non-responders. Notably, a higher percentage of responders had elevated infliximab trough levels compared to non-responders, although this difference was not statistically significant. Additionally, a strong correlation was observed between anti-infliximab antibodies and markers of inflammation such as CRP and rheumatoid factor. Importantly, smoking emerged as a negative predictor of responsiveness to infliximab therapy. These findings highlight the complex interplay between biological markers and treatment outcomes in rheumatoid arthritis, warranting further investigation.

References

1. Zhang Q, Liu Q, Lin C, Baima Y, Li H, Gong H, et al. The prevalence of rheumatoid arthritis in middle-aged and elderly people living in Naqu City, Tibet, Autonomous Region of China. J Orthop Surg Res 2020;15:388
2. Tabin S, Gupta RC, kamili AN, parray JA. Medical and medicinal importance of Rheum spp. collected from different altitudes of the Kashmir Himalayan range. Cell Mol Biomed Rep 2022;2:187-201.
3. Koch AE. The pathogenesis of rheumatoid arthritis. Am J Orthop (Belle Mead NJ) 2007;36:5-8.
4. Kallam SDM, Bodapati A, Reddy AS, Reddy KTK. Bioanalytical method development for monoclonal

antibodies: advances and challenges. Cell Mol Biomed Rep 2025;5:48-62.
5. Barlow NL, Mohammed P, Berg JD. Serum trough infliximab and anti-infliximab antibodies in a cohort of gastroenterology and rheumatology patients' infliximab therapeutic drug monitoring. Ann Clin Biochem 2016;53:477-84.
6. Lim SH, Kim K, Choi CI. Pharmacogenomics of Monoclonal Antibodies for the Treatment of Rheumatoid Arthritis. J Pers Med 2022;12:1265.
7. Nozaki Y, Kotani T, Takeuchi T, Hidaka T, Miyake H, Hatta K, et al. The Impact of Early Optimization of Infliximab Blood Concentrations >1 mug/mL on Therapeutic Effectiveness in Rheumatoid Arthritis. Front Biosci (Landmark Ed) 2023;28(4):68.
8. Thudium CS, Frederiksen P, Karsdal MA, Bay-Jensen AC. Changes in type VI collagen degradation reflect clinical response to treatment in rheumatoid arthritis patients treated with tocilizumab. Arthritis Res Ther 2024;26:3.
9. Yang X, Cai Y, Xue B, Zhang B. Diagnostic value of anti-cyclic citrullinated peptide antibody combined with rheumatoid factor in rheumatoid arthritis in Asia: a meta-analysis. J Int Med Res 2021;49:03000605211047714.
10. Catrina AI, Joshua V, Klareskog L, Malmström V. Mechanisms involved in triggering rheumatoid arthritis. Immunol Rev 2016;269:162-74.
11. Al-Osami MH, Allawi A, Al-Saadawi TH. The association of smoking with the extra-articular manifestations in rheumatoid arthritis patients. Iraqi Postgrad Med J 2013;12:146-52.
12. Mattey DL, Hutchinson D, Dawes PT, Nixon NB, Clarke S, Fisher J, et al. Smoking and disease severity in rheumatoid arthritis: association with polymorphism at the glutathione S-transferase M1 locus. Arthritis Rheum 2002;46:640-6.
13. Klareskog L, Malmström V, Lundberg K, Padyukov L, Alfredsson L. Smoking, citrullination and genetic variability in the immunopathogenesis of rheumatoid arthritis. Semin Immunol 2011;23:92-8.
14. Frade-Sosa B, Ponce A, Ruiz-Esquide V, García-Yébenes MJ, Morlá R, Sapena N, et al. High sensitivity C reactive protein in patients with rheumatoid arthritis treated with antibodies against IL-6 or Jak inhibitors: a clinical and ultrasonographic study. Diagnostics (Basel) 2022;12:182.
15. de Hair MJ, Landewé RB, van de Sande MG, van Schaardenburg D, van Baarsen LG, Gerlag DM, et al. Smoking and overweight determine the likelihood of developing rheumatoid arthritis. Ann Rheum Dis 2013;72:1654-8.
16. Seror R, Henry J, Gusto G, Aubin HJ, Boutron-Ruault M-C, Mariette X. Passive smoking in childhood increases the risk of developing rheumatoid arthritis. Rheumatology (Oxford) 2019;58:1154-62.
17. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69:70-81.
18. Söderlin M, Petersson I, Geborek P. The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug. Scand J Rheumatol 2012;41:1-9.
19. Song IS, Sohn HS, Kim H, Lim E, Kwon M, Ha JH, et al. Impact of smoking on the effectiveness of TNF-α inhibitors in patients with rheumatoid arthritis or Crohn's disease. Transl Clin Pharmacol 2014;22:92-101.
20. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun 2010;34:J258-J65.
21. Shrivastava AK, Singh H, Raizada A, Singh S, Pandey A, Singh N, et al. Inflammatory markers in patients with rheumatoid arthritis. Allergol Immunopathol (Madr) 2015;43:81-7.
22. Dessie G, Tadesse Y, Demelash B, Genet S, Malik T, Dejenie TA. Evaluation of C-reactive protein and associated factors among patients suffering from rheumatoid arthritis at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Open Access Rheumatol 2021;13:247-55.
23. Rocha SdB, Baldo DC, Andrade LEC. Clinical and pathophysiologic relevance of autoantibodies in rheumatoid arthritis. Adv Rheumatol 2019;59:2.
24. van Schouwenburg P. Antibodies against antibodies: immunogenicity of adalimumab as a model. Ann Rheum Dis 2012.
25. Bobbio-Pallavicini F, Caporali R, Alpini C, Avalle S, Epis OM, Klersy C, et al. High IgA rheumatoid factor levels are associated with poor clinical response to tumour necrosis factor α inhibitors in rheumatoid arthritis. Ann Rheum Dis 2007;66:302-7.
26. Albarzinji N, Ismael SA, Albustany D. Association of rheumatoid arthritis and its severity with human leukocytic antigen-DRB1 alleles in Kurdish region in North of Iraq. BMC Rheumatol 2022;6:1-5.
27. Alessandri C, Bombardieri M, Papa N, Cinquini M, Magrini L, Tincani A, et al. Decrease of anti-cyclic citrullinated peptide antibodies and rheumatoid factor following anti-TNFα therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement. Ann Rheum Dis 2004;63:1218-21.
28. Kobak S, Bes C. An autumn tale: geriatric rheumatoid arthritis. Ther Adv Musculoskelet Dis 2018;10:3-11.
29. Quistrebert J, Hässler S, Bachelet D, Mbogning C, Musters

A, Tak PP, et al., editors. Incidence and risk factors for adalimumab and infliximab anti-drug antibodies in rheumatoid arthritis: a European retrospective multicohort analysis. Semin Arthritis Rheum 2019;48:967-75.

30. Ingegnoli F, Castelli R, Gualtierotti R. Rheumatoid factors: clinical applications. Dis Markers 2013;35:727-34.
31. Perilla AMD, Vásquez GM, Rojas MX. ¿ Is seropositivity in patients with rheumatoid arthritis treated with adalimumab a factor to develop anti-adalimumab antibodies? Rev Cient Reumatologia (English Edition). 2019;26:24-30.
32. Larid G, Pancarte M, Offer G, Clavel C, Martin M, Pradel V, et al. In rheumatoid arthritis patients, HLA-DRB1* 04: 01 and rheumatoid nodules are associated with ACPA to a particular fibrin epitope. Front Immunol 2021;12:692041.
33. Eker YÖ, Pamuk ÖN, Pamuk GE, Dönmez S, Çakır N. The Frequency of anti-CCP antibodies in patients with rheumatoid arthritis and psoriatic arthritis and their relationship with clinical features and parameters of angiogenesis: A comparative study. Eur J Rheumatol 2014;1:67-71.