ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2024.69188
Rheumatology Quarterly 2024;2(1):19-24

THE EFFECT OF TNF-ALPHA INHIBITORS USED IN RHEUMATOLOGIC DISEASES ON HEMATOLOGICAL PARAMETERS

Rabia Pişkin Sağır[1], Servet Yolbaş[2], Yurdagül Sağır Danacı[3], Ahmet Karataş[4]

[1]Tatvan State Hospital, Clinic of Rheumatology, Bitlis, Turkey
[2]İnönü University Faculty of Medicine, Department of Rheumatology, Malatya, Turkey
[3]İnönü University Faculty of Medicine, Department of Medical Oncology, Malatya, Turkey
[4]Fırat University Faculty of Medicine, Department of Rheumatology, Elazığ, Turkey

Abstract

Aim: Tumor necrosis factor (TNF) inhibitors are used in patients resistant to conventional treatments for rheumatologic diseases such as rheumatoid arthritis (RA) and spondyloarthropathy (SpA). Agents used for treating rheumatic diseases affect hematological parameters. In this study, we evaluated hematological parameters in patients with inflammatory rheumatic diseases who started anti-TNF treatment at our center.

Material and Methods: A total of 109 patients diagnosed with RA, SpA without psoriatic arthritis (PsA) and PsA who applied to the İnönü University Rheumatology Clinic and started TNF inhibitor treatment were included in the study. The patients' diagnoses, demographic data such as age and gender, and laboratory parameters (white blood cell, eosinophil, lymphocyte, monocyte, neutrophil counts, hemoglobin, platelet (PLT), mean platelet volume (MPV) ratio, neutrophil to lymphocyte ratio, monocyte/lymphocyte ratio and eosinophil/lymphocyte ratio) at the beginning of treatment and at the first month of treatment were recorded.

Results: The rheumatic inflammatory patients included in our study comprised 29 RA, 16 PsA, and 64 spondyloarthritis without PsA patients. Seventy-seven patients were female (70.6%), and 32 were male (29.4%), with a mean age of 46 (18-78). When all patients were evaluated together, a statistically significant decrease in white blood cell, neutrophil, and PLT counts, a statistically significant increase in hemoglobin, lymphocyte, and eosinophil counts, and a statistically significant decrease in neutrophil to lymphocyte and monocyte to lymphocyte ratios with an increase in MPV and mean platelet volume to platelet count were observed at the 1st month of treatment. No complications related to laboratory changes were observed, and no patient discontinued treatment.

Conclusion: Although there were changes in hematological parameters in patients receiving TNF inhibitor treatment in our study, we believe that regular hemogram monitoring should be performed at regular intervals in patients undergoing anti-TNF treatment, despite the absence of any complications in our study, as cases of severe cytopenia and eosinophilia have been reported in the literature following TNF inhibitor treatment.

Keywords: Spondyloarthritis, psoriatic arthritis, rheumatoid arthritis, hematological parameters, NLR ratio, anti-TNF agents

INTRODUCTION

Tumor necrosis factor-alpha (TNF-α) is a bell-shaped trimeric glycoprotein comprising 212 amino acids. It is primarily produced by monocytes and macrophages and exhibits a broad spectrum of biological effects (1). TNF-α plays crucial roles in natural or acquired immunity, cachexia, endotoxic shock, inflammation,

Address for Correspondence: Rabia Pişkin Sağır, Tatvan State Hospital, Clinic of Rheumatology, Bitlis, Turkey
Phone: +90 538 725 77 47 **E-mail:** piskinrabia@hotmail.com **ORCID ID:** orcid.org/0000-0003-1791-790X
Received: 30.12.2023 **Accepted:** 13.02.2024

tissue remodeling, infection and immunity, cytotoxicity, and apoptosis (1). Agents that inhibit TNF-α, such as anti-TNF agents, are used in rheumatic diseases resistant to conventional treatment, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and inflammatory bowel diseases (2). TNF-α blockade can be employed in pathologies associated with increased TNF-α expression. Anti-TNF drugs can be produced in the form of monoclonal antibodies or fusion proteins targeting this cytokine (1).

Various side effects of anti-TNF treatments have been reported in clinical applications, including injection site reactions, infusion reactions, infections, cytopenia, demyelinating diseases, heart failure, increased autoimmune diseases, pulmonary fibrosis, and liver toxicity (3). Although current guidelines do not mandate regular hemogram monitoring because hematological side effects were not reported shortly after the release of these drugs, non-malignant hematological side effects such as profound neutropenia, thrombocytopenia, pancytopenia, and hypercoagulable eosinophilia have been reported in the literature during treatment (4).

Furthermore, the specific parameters derived from the ratio of certain parameters in these blood count tests were correlated with various systemic disease clinics. Relationships between hematological indices, such as mean platelet volume to platelet count ratio (MPR), neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and eosinophil to lymphocyte ratio (ELR), and the survival of various malignancies have been demonstrated. Different cells play dominant roles in the pathogenesis of different rheumatic diseases; therefore, these cell ratios are expected to be associated with disease clinics in clinical practice. Recent studies have shown the relationship between these indices and the clinical symptoms and disease activities of various rheumatic diseases (5-7).

In our study, we aimed to evaluate the impact of anti-TNF treatments used for treating inflammatory rheumatic diseases on hematological parameters and the hematological indices derived from these parameters.

MATERIAL AND METHODS

Ethical approval for our study was obtained from the İnönü University Scientific Research and Publication Ethics Committee under protocol number 2019/243. Subsequently, we retrospectively analyzed the data of 109 patients diagnosed with RA, spondyloarthropathy without PsA (non-PSA SpA), and PsA who applied to the İnönü University Faculty of Medicine, Rheumatology Outpatient Clinic and initiated anti-TNF (infliximab, adalimumab, etanercept, certolizumab, and golimumab) treatment for the first time at our center.

Hemogram parameters of the patients at the initiation of anti-TNF treatment and at the 1st month after treatment were examined. Hemogram parameters included white blood cell count, eosinophil count, lymphocyte count, monocyte count, neutrophil count, hemoglobin level, PLT count, MPV, and ratios such as MPR, NLR, MLR, and ELR.

Statistical Analysis

Statistical analysis were performed using the SPSS 22 statistical program (IBM Corp., Armonk, N.Y., USA). Data are presented as mean ± standard deviation. Paired samples t-test was employed for the analysis of dependent variables, with $p<0.05$ considered statistically significant.

RESULTS

A total of 109 patients were included in our study. Of these, 77 were female (70.6%) and 32 were male (29.4%). Sixty-four patients were diagnosed with non-PSA SpA, 29 with RA, and 16 with PsA. The average age was 46 (18-78). Adalimumab was the most commonly initiated treatment in 46 patients (42.2%), followed by golimumab in 31 patients (28.4%), etanercept in 27 patients (24.8%), certolizumab in 3 patients (2.8%), and infliximab in 2 patients (1.8%). The baseline characteristics of the patients and the values of hematological parameters at the initiation of treatment and at the first month are presented in Table 1.

In our study, there were statistically significant decreases in white blood cell count, neutrophil count, PLT, and NLR and MLR ratios at the first month compared with baseline values for all treatment agents. In addition, there were statistically significant increases in hemoglobin, eosinophil count, lymphocyte count, MPV, and MPR values. In addition to these values, there was a statistically nonsignificant increase in monocyte count and ELR value (Table 1). Furthermore, all data were separately analyzed within disease subgroups (Table 2-4). In patients with RA, there was a statistically significant increase in eosinophil and lymphocyte counts and a statistically significant decrease in PLT. No statistically significant changes were observed in the other parameters (Table 2). In the non-PSA SpA group, there was a statistically significant increase in lymphocyte count and a statistically significant decrease in neutrophil and PLT. Consequently, an increase in the MPV/PLT ratio and a statistically significant decrease in the NLR and MLR ratios were observed (Table 3). In the PsA patient group, in addition to the changes observed in the non-PSA SpA group, a statistically significant decrease in white blood cell count was noted (Table 4).

Table 1. Changes in hematological parameters at the initiation and first month of anti-TNF treatment in all patients

Parameter	Baseline value (mean ± SD)	Post-treatment 1st month (mean ± SD)	p-value
Leukocyte (10^9/L)	8.29±2.13	7.89±1.82	0.027
Eosinophil (10^9/L)	0.17±0.28	0.21±0.15	0.020
Lymphocyte (10^9/L)	2.33±0.68	2.61±0.76	<0.001
Monocyte (10^9/L	0.67±0.21	0.67±0.20	0.968
Neutrophil (10^9/L)	5.00±1.90	4.34±1.64	<0.001
Hemoglobin (g/dL)	13.13±0.15	13.35±0.16	0.007
Platelet (10^{12}/L)	308.7±75.3	286.9±61.2	<0.001
MPV (fL)	10.45±0.89	10.54±0.84	0.037
MPV/platelet ratio	0.0362±0.01071	0.0388±0.01038	<0.001
NLR	2.38±1.38	1.91±1.40	<0.001
MLR	0.31±0.13	0.28±0.13	0.004
ELR	0.07±0.05	0.08±0.05	0.751

p-values were considered statistically significant if <0.05, TNF: Tumor necrosis factor, SD: Standard deviation, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio

Table 2. Changes in hematological parameters at the initiation and 1st month of anti-TNF treatment in patients with rheumatoid arthritis

Parameter	Baseline value (mean ± SD)	Post-treatment 1st month (mean ± SD)	p-value
Leukocyte (10^9/L)	8.05±2.39	8.02±2.30	0.923
Eosinophil (10^9/L)	0.16±0.12	0.23±0.18	0.005
Lymphocyte (10^9/L)	2.06±0.66	2.28±0.77	0.041
Monocyte (10^9/L)	0.70±0.22	0.70±0.23	0.899
Neutrophil (10^9/L)	4.97±2.23	4.73±2.33	0.540
Hemoglobin (g/dL)	12.46±0.27	12.63±0.30	0.391
Platelet (10^{12}/L)	321.03±84.24	304.65±64.51	0.071
MPV (fL)	10.45±1.00	10.45±0.82	1.000
MPV/platelet ratio	0.0349±0.0103	0.0360±0.0089	0.299
NLR	2.64±1.63	2.57±2.29	0.811
MLR	0.36±0.14	0.34±0.18	0.498
ELR	0.08±0.052	0.09±0.05	0.042

p-values were considered statistically significant if <0.05, TNF: Tumor necrosis factor, SD: Standard deviation, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio

DISCUSSION

Anti-TNF therapies have emerged as a significant treatment option for rheumatic diseases. Beyond their clinical effects, researchers are increasingly interested in their impact on bone marrow stem cells and, consequently, hematological parameters (8-10). TNF is known as a proinflammatory cytokine and can affect homeostasis in the bone marrow microenvironment. Depending on the cytokine microenvironment and its own concentration, TNF can exert stimulatory or inhibitory effects on the growth of hematopoietic progenitors. While TNF-α has been shown to have a stimulatory effect on granulocyte colony-stimulating factor, erythropoietin, and stem cell factor, it has been shown to have an inhibitory effect on granulocyte-macrophage colony-stimulating factor and interleukin (IL)-3 in other studies. In addition, various proinflammatory cytokines such as IL-1, IL-6, and IL-8 are known to be affected by TNF-α. Therefore, theoretically, inhibition of TNF-α may lead to bone marrow insufficiency by blocking stem cell differentiation (8). A correlation between TNF-α levels and the development

Table 3. Changes in hematological parameters at the initiation and 1st month of anti-TNF treatment in patients with spondyloarthritis without psoriatic arthritis

Parameter	Baseline value (mean ± SD)	Post-treatment 1st month (mean ± SD)	p-value
Leukocyte (10^9/L)	8.26±2.05	8.01±1.69	0.214
Eosinophil (10^9/L)	0.18±0.12	0.19±0.13	0.277
Lymphocyte (10^9/L)	2.44±0.70	2.77±0.75	<0.001
Monocyte (10^9/L)	0.63±0.19	0.66±0.19	0.260
Neutrophil (10^9/L)	4.94±1.83	4.31±1.35	0.002
Hemoglobin (g/dL)	13.34±0.21	13.52±0.21	0.050
Platelet (10^{12}/L)	306.00±74.98	282.96±62.13	<0.001
MPV (fL)	10.47±0.84	10.53±0.84	0.154
MPV/platelet ratio	0.0367±0.0113	0.0395±0.0113	0.002
NLR	2.26±1.35	1.70±0.85	<0.001
MLR	0.28±0.13	0.25±0.10	0.005
ELR	0.07±0.05	0.07±0.04	0.574

p-values were considered statistically significant if <0.05, TNF: Tumor necrosis factor, SD: Standard deviation, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio

Table 4. Changes in hematological parameters at the initiation and 1st month of anti-TNF treatment in patients with psoriatic arthritis

Parameter	Baseline value (mean ± SD)	Post-treatment (mean ± SD)	p-value
Leukocyte (10^9/L)	8.84±1.95	7.16±1.11	0.008
Eosinophil (10^9/L)	0.17±0.16	0.17±0.12	0.983
Lymphocyte (10^9/L)	2.37±0.55	2.53±0.63	0.283
Monocyte (10^9/L)	0.73±0.24	0.65±0.18	0.175
Neutrophil (10^9/L)	5.32±1.58	3.74±0.91	0.003
Hemoglobin (g/dL)	13.48±0.38	13.95±0.36	0.34
Platelet (10^{12}/L)	297.18±59.51	271.00±45.24	0.013
MPV (fL)	10.35±0.92	10.71±0.89	0.007
MPV/platelet ratio	0.0364±0.0088	0.0407±0.0079	0.018
NLR	2.35±0.93	1.57±0.52	0.004
MLR	0.32±0.10	0.26±0.08	0.049
ELR	0.07±0.06	0.07±0.05	0.759

p-values were considered statistically significant if <0.05, TNF: Tumor necrosis factor, SD: Standard deviation, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio

of neutropenia in patients receiving chemotherapy for acute leukemia was demonstrated in a study by Bruserud et al. (10).

Although rare, hematological side effects such as thrombocytopenia, neutropenia, pancytopenia, and aplastic anemia, which can sometimes result in death, have been reported in patients receiving anti-TNF treatment. In a post-marketing cohort study by Feltelius et al. (11), approximately half of the 17 patients receiving etanercept developed serious hematological reactions. However, another study by Miehsler et al. (12) reported a generally low incidence of hematological side effects in patients receiving infliximab. Cases of pancytopenia and aplastic anemia have been reported using both etanercept and infliximab (13-16). In another study by Yazdani et al. (17), 12% of 130 patients receiving anti-TNF treatment developed non-infection-related cytopenia, predominantly leukopenia, but these cytopenias were transient and did not require hematological monitoring. In our study, although there was a statistically significant decrease in white blood cell and neutrophil counts

in patients after anti-TNF treatment, no patient had leukopenia or neutropenia requiring discontinuation of the drug. However, despite the lack of clinical significance, there was a statistically significant increase in hemoglobin levels, possibly related to the suppression of inflammation.

Eosinophilia after anti-TNF treatment has also been reported. Cancelliere et al. (18) reported a case of subacute prurigo with marked eosinophilia after infliximab administration in an 80-year-old patient with RA. The relationship between TNF inhibition and eosinophilia was confirmed in this case because both prurigo and eosinophilia significantly improved after discontinuation of the drug but recurred when another TNF inhibitor, etanercept, was started (18). In our study, especially in patients with RA, there was a statistically significant increase in eosinophil count after treatment.

In recent years, the NLR and platelet-lymphocyte ratio (PLR) have been shown to be systemic inflammation markers associated with the prognosis of many cardiovascular diseases, malignancies, and chronic inflammatory diseases. Additionally, NLR and PLR are related to erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IL-6, and TNF-α (19-21). In a study evaluating NLR ratios after anti-TNF treatment in RA and AS patients, NLR was correlated with disease activity score 28 (DAS 28), ESR, and CRP in RA patients and with bath AS disease activity index, ESR, and CRP in AS patients (5). In another study examining NLR in patients with psoriasis and PsA, NLR was significantly correlated with PASI scores, and a high NLR ratio was found to be a predictor for the development of PsA in patients with psoriasis (7). In our study, although disease activities were not evaluated, NLR and MLR ratios, indicative of systemic inflammatory response, decreased after anti-TNF treatment, showing a negative correlation with the inflammatory process, and the MPV, indicative of platelet function activity, increased. Because of the increase in MPV and decrease in platelet count, MPR also increased. These results suggest that anti-TNF treatment agents are effective in suppressing inflammation.

Our study has limitations due to its retrospective nature, the small number of included patients, and the evaluation of only the first-month data of the patients. Although the clinical and laboratory activations of patients were not individually assessed at the beginning and after treatment, biological therapies were initiated during the active disease period. In addition, in our study, changes in the hemogram parameters induced by anti-TNF therapies were investigated; hence, the first-month hemogram parameters were evaluated without altering the current treatments of the patients.

CONCLUSION

In conclusion, patients receiving TNF-α inhibitors are closely monitored for diseases such as malignancy, hepatitis B, and tuberculosis; however, current guidelines do not provide clear information regarding hematological monitoring. Although our study did not reveal significant changes in hematological parameters after anti-TNF treatment that would necessitate discontinuation or cessation of treatment, serious hematological reactions such as severe leukopenia, neutropenia, thrombocytopenia, and eosinophilia have been reported in the literature after anti-TNF treatment. Therefore, prospective studies with a larger number of patients, evaluating disease activity scales, and having a longer follow-up period are required to comprehensively assess the efficacy and side effects of anti-TNF treatment agents in rheumatic diseases.

Ethics

Ethics Committee Approval: Ethical approval for our study was obtained from the İnönü University Scientific Research and Publication Ethics Committee under protocol number 2019/243.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: R.P.S., S.Y., Y.S.D., A.K., Concept: R.P.S., S.Y., Design: R.P.S., S.Y., Y.S.D., A.K., Data Collection or Processing: R.P.S., S.Y., Y.S.D., Analysis or Interpretation: R.P.S., S.Y., Literature Search: R.P.S., S.Y., A.K., Writing: R.P.S., S.Y., A.K.,

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Willrich MA, Murray DL, Snyder MR. Tumor necrosis factor inhibitors: clinical utility in autoimmune diseases. Transl Res 2015;165:270-82.
2. Schuna AA, Megeff C. New drugs for the treatment of rheumatoid arthritis. Am J Health Syst Pharm 2000;57:225-34.
3. Kirkham B, Furst DE, Romain PL. Tumor necrosis factor-alpha inhibitors: an overview of adverse effects. UpToDate, Waltham, MA (2016).
4. Bessissow T, Renard M, Hoffman I, et al. Review article: non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. Aliment Pharmacol Ther 2012;36:312-23.
5. Enginar AU, Kacar C. Neutrophil-lymphocyte and platelet-lymphocyte rate and their seasonal differences in ankylosing spondylitis and rheumatoid arthritis patients using anti-TNF medication. Bratisl Lek Listy 2019;120:586-92.

6. Gökmen F, Akbal A, Reşorlu H, et al. Neutrophil-lymphocyte ratio connected to treatment options and inflammation markers of ankylosing spondylitis. J Clin Lab Anal 2015;29:294-8.

7. Kim DS, Shin D, Lee MS, et al. Assessments of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in Korean patients with psoriasis vulgaris and psoriatic arthritis. J Dermatol 2016;43:305-10.

8. Jacobsen SE, Jacobsen FW, Fahlman C, et al. TNF-alpha, the great imitator: role of p55 and p75 TNF receptors in hematopoiesis. Stem Cells 1994;12(Suppl 1):126-8.

9. Keystone EC. Tumor necrosis factor-alpha blockade in the treatment of rheumatoid arthritis. Rheum Dis Clin North Am 2001;27:427-43.

10. Bruserud O, Bergheim J, Shammas FV, et al. Serum concentrations of tumour necrosis factor-alpha during chemotherapy-induced leukopenia in patients with acute leukaemia and bacterial infections. Leuk Res 1994;18:415-21.

11. Feltelius N, Fored CM, Blomqvist P, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis 2005;64:246-52.

12. Miehsler W, Novacek G, Wenzl H, et al. A decade of infliximab: the Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. J Crohns Colitis 2010;4:221-56.

13. Szalay B, Acs L, Vásárhelyi B, et al. Successful use of tocilizumab in a patient with rheumatoid arthritis following severe pancytopenia during etanercept therapy. J Clin Rheumatol 2011;17:377-9.

14. Kuruvilla J, Leitch HA, Vickars LM, et al. Aplastic anemia following administration of a tumor necrosis factor-alpha inhibitor. Eur J Haematol 2003;71:396-8.

15. Menon Y, Cucurull E, Espinoza LR. Pancytopenia in a patient with scleroderma treated with infliximab. Rheumatology (Oxford) 2003;42:1273-4.

16. Marchesoni A, Arreghini M, Panni B, et al. Life-threatening reversible bone marrow toxicity in a rheumatoid arthritis patient switched from leflunomide to infliximab. Rheumatology (Oxford) 2003;42:193-4.

17. Yazdani R, Simpson H, Kaushik VV. Incidence of cytopoenias with anti-TNF alpha therapy. In: Rheumatology. Great Clarendon St, Oxford OX2 6DP, England: Oxford Univ Press; 2007.

18. Cancelliere N, Barranco P, Vidaurrázaga C, et al. Subacute prurigo and eosinophilia in a patient with rheumatoid arthritis receiving infliximab and etanercept. J Investig Allergol Clin Immunol 2011;21:248-9.

19. Buyukkaya E, Karakas MF, Karakas E, et al. Correlation of neutrophil to lymphocyte ratio with the presence and severity of metabolic syndrome. Clin Appl Thromb Hemost 2014;20:159-63.

20. Imtiaz F, Shafique K, Mirza SS, et al. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med 2012;5:2.

21. Hamminga EA, van der Lely AJ, Neumann HA, Thio HB. Chronic inflammation in psoriasis and obesity: implications for therapy. Med Hypotheses 2006;67:768-73.