ORIGINAL ARTICLE

THE RELATIONSHIP BETWEEN TOCILIZUMAB USE AND EOSINOPHIL COUNT IN PATIENTS WITH RHEUMATOID ARTHRITIS: A RETROSPECTIVE STUDY

Romatoid Artritli Hastalarda Tosilizumab Kullanımı ile Eozinofil Sayısı Arasındaki İlişki: Retrospektif Bir Çalışma

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ABSTRACT

Objective: This study aimed to determine the relationship between tosilizumab use and eosinophil counts in patients with rheumatoid arthritis.

Material and Methods: Thirty five patients diagnosed with rheumatoid arthritis (RA) receiving either synthetic disease-modifying antirheumatic drugs (DMARDs) or tocilizumab treatment were included in this study. Patient age and disease duration, disease activity parameters and eosinophil values were recorded.

Results: Comparing the eosinophil counts and percentages of the DMARD group with the Tocilizumab group, any statistically significant differences were found. There was no significant difference in eosinophil counts and percentages in the DMARD group in repeated measurements. However, in the Tocilizumab group, there was a significant difference in both parameters.

Conclusion: A significant increase in eosinophil counts was observed in the group receiving tocilizumab therapy at the 1st month. Therefore, during treatment monitoring, especially in the early stages, attention should also be paid to eosinophil values.

Keywords: *Rheumatoid Arthritis; Tocilizumab; Eosinophil Count.*

ÖZET

Amaç: Bu çalışmada romatoid artritli hastalarda tosilizumab kullanımı ile eozinofil sayısı arasındaki ilişkinin incelenmesi amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya, sentetik hastalık modifiye edici antiromatizmal ilaçlar (DMARD) veya tosilizumab tedavisi alan, romatoid artrit (RA) tanılı 35 hasta dahil edildi. Hastaların yaşı, hastalık süreleri, hastalık aktivite parametreleri ve eozinofil değerleri kaydedildi.

Bulgular: DMARD grubunun eozinofil sayısı ve yüzdeleri Tocilizumab grubuyla karşılaştırıldığında istatistiksel olarak anlamlı bir fark bulunamadı. Grup içi karşılaştırmalarda DMARD grubunda tekrarlanan ölçümlerde eozinofil sayısı ve yüzdelerinde anlamlı fark saptanmazken, Tocilizumab grubunda her iki parametrede de anlamlı farklılık vardı.

Sonuç: Bu çalışmada tocilizumab tedavisi alan hastalarda 1. ayda eozinofil sayısında anlamlı artış gözlendi. Bu nedenle tedavi takibi sırasında özellikle erken dönemde eozinofil değerlerine dikkat edilmelidir.

Anahtar Kelimeler: *Romatoid Artrit; Tosilizumab; Eozinofil Sayısı.*

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INTRODUCTION

Eosinophilia, although it varies depending on laboratory standards, is defined as having an absolute eosinophil count above 500/mm³ in circulation. Eosinophil percentages above 5% are also considered eosinophilia in most centers, however, an accurate eosinophilia diagnosis typically requires the calculation of the absolute eosinophil count. Eosinophilia is classified as mild (up to 1500/mm³), moderate (1500-5000/mm³), and severe (above 5000/mm³) (1). In patients with persistent, unexplained eosinophilia, a detailed investigative process should be initiated to elucidate the etiology.

There may be many causes of eosinophilia, and the etiology is classified within three main categories: primary (characterized by clonal eosinophilia hematologic neoplasms), secondary (reactive) eosinophilia causes, and idiopathic (cases where neither primary nor secondary causes of eosinophilia can be identified). Secondary causes typically underlie eosinophilia in the majority of cases. Among them, the most common are allergic diseases and conditions (drug hypersensitivity), parasitic infections, and rheumatologic-autoimmune diseases (2).

Eosinophilia is often seen in some rheumatologic diseases (such as Churg-Strauss, IgG4-related disease, and diffuse eosinophilic fasciitis) and is defined as part of the clinical-pathophysiological process. In other rheumatologic diseases where eosinophilia is rare, secondary causes should primarily be investigated, especially inquiring about the medications being used (3). Recently, the use of tocilizumab, a monoclonal IL-6 receptor antagonist, has yielded positive results in the treatment of rheumatoid arthritis. As a relatively new treatment option compared to synthetic disease-modifying antirheumatic drugs (DMARDs), tocilizumab has some unknown aspects. Cases of eosinophilia associated with tocilizumab treatment have been reported in the literature (4-8). In this study, it is aimed to investigate whether there was any difference in eosinophil values in patients diagnosed with rheumatoid arthritis receiving synthetic DMARDs or tocilizumab treatment for one year.

MATERIAL AND METHODS

This retrospective study included 35 patients (2 males, 33 females) diagnosed with rheumatoid arthritis (RA) according to the ACR/EULAR 2010 Rheumatoid Arthritis classification criteria, who were receiving synthetic disease-modifying antirheumatic drugs (DMARDs) or tocilizumab treatment. Patient age and disease duration, DAS28 scores (at 0, 3, 6, and 12 months), ESR and CRP levels, eosinophil counts and percentages (at 0, 1, 3, 6, and 12 months) were recorded. Laboratory results and clinical assessments were performed on the same visit day. DAS28 is a scale that evaluates disease activity by combining the presence of swelling and tenderness in 28 joints commonly affected by RA, along with ESR and the patient's overall health assessment through a mathematical calculation. Disease activity is categorized based on calculated DAS28 scores as remission (<2.6), low disease activity (2.6-3.2), moderate activity (3.2-5.2), or high disease activity (>5.2).

This study was approved by Haydarpaşa Numune Research and Training Hospital Ethics Committee (approval code: HNHAH-KAEK 2021/27).

Statistical analysis: IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) was used for the analysis. Descriptive statistics were expressed as median, minimum, and maximum values. The Shapiro-Wilk test was used to assess whether the study groups followed a normal distribution. Since the data did not follow a normal distribution, quantitative data between groups were analyzed using the Mann-Whitney U test. The change in repeated quantitative measurements over time was assessed using Friedman's two-way analysis of variance. The Bonferroni-adjusted Wilcoxon test was used to determine which repeated measurements contributed to statistically significant changes. A p-value below 0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 58.09 years (range: 29-89), and the duration of the disease was 122.77 months (range: 3-336). The DMARD group had a mean patient age of 58.22 years (range: 43-89), compared to 57.94 years in the Tocilizumab group. (range: 29-70). The mean disease duration within the DMARD group was 100.83 months (range: 3-336), compared to 146 months in the Tocilizumab group (range: 24-312). There were no statistically significant differences between the

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groups for these two parameters (p=0.463 and p=0.089, respectively). Out of the patients, 51.4% (n=18) were receiving DMARD treatment, and 48.6% (n=17) were receiving tocilizumab treatment. In the DMARD-treated group, 8 patients were on methotrexate, 4 on leflunomide, 2 on methotrexate + leflunomide, 2 on methotrexate + hydroxychloroquine, 1 was on sulfasalazine + hydroxychloroquine, and 1 on hydroxychloroquine alone. In both groups, 6 patients were using corticosteroids in addition to their current treatment. There was no significant difference between the two groups in terms of the number of patients receiving corticosteroid (p=0.592). In the Tocilizumab group, 35.3% (n=6) of patients had previously received an anti-TNF treatment. When all parameters were compared between the two groups, only DAS28 values showed a significant difference. DAS28 values were significantly lower in the DMARD group at baseline, 3 months, and 6 months, while at 12 months, this trend shifted in favor of the Tocilizumab group. When the eosinophil counts and percentages of the DMARD group were compared with the 0-1-3-6-12-month values of the Tocilizumab group, any statistically significant differences were found. In intra-group comparisons, there was no significant difference in eosinophil counts and percentages in the DMARD group in repeated measurements. However, in the Tocilizumab group, there was a significant difference in both parameters. Upon further investigation into the origins of this divergence, it was found that eosinophil counts at baseline were significantly lower than the values at 3, 6, and 12 months (p=0.008, p=0.033, p=0.032, respectively), and the values at 1 month were also significantly lower than those at 3 months (p=0.03). In terms of eosinophil percentages, there was a significant difference between the baseline values and the values at 1, 3, 6, and 12 months (p=0.035, p=0.004, p=0.015, p=0.005, respectively). All intra-group and inter-group comparisons are presented in Table 1. The eosinophil counts and percentages in the Tocilizumab group is shown in Figure 1.

DISCUSSION

In rare rheumatological conditions, such as rheumatoid arthritis, where eosinophilia is infrequently encountered, when patients present with this condition, a comprehensive evaluation should primarily encompass an inquiry into their medication usage, allergic diseases, parasitic infections, hematological disorders, or potential alternative diagnoses related to eosinophilia (9).

Studies have demonstrated a wide-ranging prevalence of eosinophilia in rheumatoid arthritis (RA), spanning from 3.2% to 21.6% (9-12). This broad range likely results from methodological variations across studies. In one study involving 298 patients with detected eosinophilia, the cause of eosinophilia is determined in only 159 patients, with drugs being implicated in 74.2% of these cases (13). Another study also reported a close association between eosinophilia and medical treatment in rheumatological diseases (14). Furthermore, there are numerous case reports in the literature describing the development of eosinophilia in RA patients related to drug use, including a limited number of cases associated with tocilizumab. The first case was reported in 2010 by Morrisroe and Wong. In this case, a patient diagnosed with rheumatoid arthritis and initiated on tocilizumab therapy developed epigastric pain in the 14th week of treatment. Subsequent evaluations revealed drug-related hypereosinophilia with gastrointestinal involvement. The patient exhibited an elevation in eosinophil counts, with values reaching as high as 8800/mm^3; however, the condition ameliorated following the cessation of the medication. It was reported that eosinophil counts increased one month after the initial injection, began to decrease after three months, and monthly complete blood counts were recommended for the first three months of tocilizumab treatment (4). Other cases of eosinophilia in patients using tocilizumab for RA and Still's disease have also been reported. These cases, characterized by moderate eosinophilia, exhibited various clinical presentations such as pruritus, rashes, and gastrointestinal symptoms at different stages of tosilizumab administration (1, 3, and the 22nd application). Generally, symptom resolution and eosinophil reduction occurred upon discontinuation of the medication (5-8).

In studies evaluating the relationship between disease activity and hematologic parameters in the monitoring of rheumatoid arthritis patients, eosinophil values have generally not been assessed or significant

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Table 1. Inter and intra-group comparisons.

	DMARD	Tocilizumab	p
	Median (Min-Max)	Median (Min-Max)	
Eosinophil count (onset) (10^3/µl)	0.12 (0-0.39)	0.11 (0-0.51)	0.766
Eosinophil count (first month)	0.16 (0.09-0.62)	0.17 (0-0.24)	0.130
Eosinophil count (third month)	0.17 (0.03-0.65)	0.19 (0-0.6)	0.804
Eosinophil count (sixth month)	0.15 (0.07-0.70)	0.17 (0.01-0.34)	0.860
Eosinophil count (twelfth month)	0.14 (0.08-0.94)	0.13 (0.03-0.19)	0.512
p*	0.393	0.037	
Percentage of eosinophils (onset) (%)	1.7 (0.53-3.82)	2.0 (0.07-8.70)	0.911
Percentage of eosinophils (first month)	2.0 (0.89-5.36)	1.65 (0.07-4.70)	0.413
Percentage of eosinophils (third month)	1.96 (0.6-5.6)	2.0 (0.04-4.9)	0.874
Percentage of eosinophils (sixth month)	2.2 (0.12-5.6)	2.6 (0.19-4.9)	0.462
Percentage of eosinophils (twelfth month)	2.2 (1.3-7.4)	2.0 (0.5-4.10)	0.845
P*	0.572	0.007	
ESR (onset) (mm/hour)	43 (10-68)	31 (7-78)	0.502
ESR (first month)	28 (2-91)	13.5 (2-47)	0.085
ESR (third month)	21 (4-70)	19.5 (2-57)	0.849
ESR (sixth month)	26.5 (5-81)	17 (3-75)	0.265
ESR (twelfth month)	18 (6-88)	15 (2-56)	0.423
p*	0.008	0.03	
CRP (onset) (mg/L)	1.1 (0.1-8.8)	0.7 (0.1-2.6)	0.189
CRP (first month)	0.5 (0.1-3.10)	0.2 (0.1-3.47)	0.273
CRP (third month)	0.3 (0.1-10.9)	0.2 (0.1-4.1)	0.683
CRP (sixth month)	0.2 (0.1-1.3)	0.2 (0.1-3.4)	0.701
CRP (twelfth month)	0.4 (0.1-1.9)	0.2 (0.01-5.2)	1.000
p*	0.391	0.561	
DAS28 (onset)	1.7 (0-4.85)	4.9 (0-6.69)	0.004
DAS 28 (third month)	2.82 (1.2-3.82)	4.04 (1.6-5.93)	0.039
DAS 28 (sixth month)	2.2 (0.77-5.35)	2.66 (1.36-6.27)	0.449
DAS 28 (twelfth month)	2.78 (1.7-4.87)	2.38 (0-5.42)	0.025
p*	0.301	0.013	

DMARD=Disease modifiying anti-rheumatic drugs, ESR= Erythrocyte sedimentation rate, CRP=C-reactive protein, DAS 28=Disease activity score, $p<0.05$ statistically significant (inter-group comparison). $p^*<0.05$ statistically significant (intra-group comparison)

results have not been obtained (15-17). Furthermore, in a study assessing hematological markers in rheumatoid arthritis patients treated with tocilizumab, eosinophil counts were not included in the evaluation (18). However, a presentation at the 2014 American College of Rheumatology/Association of Rheumatology Health Professionals annual meeting reported that patients receiving tocilizumab exhibited an elevation in eosinophil percentages at the one-month interval, suggesting a potential association with the subsequent decrease in DAS28 values at 6 months.

In rheumatoid arthritis, a condition known to be associated with functional limitations, decreased quality of life, and even increased morbidity and mortality, achieving remission with prompt and efficacious treatment is of paramount importance. Hence, close monitoring of the treatment process with appropriate parameters is an essential component (19). DAS28 is widely recognized for its appropriateness in clinical applications and its ability to provide a balanced reflection of disease activity and progression across various scoring systems. (20). This study also demonstrates that DAS28 values effectively reflect the disease activity process. In the tocilizumab group,

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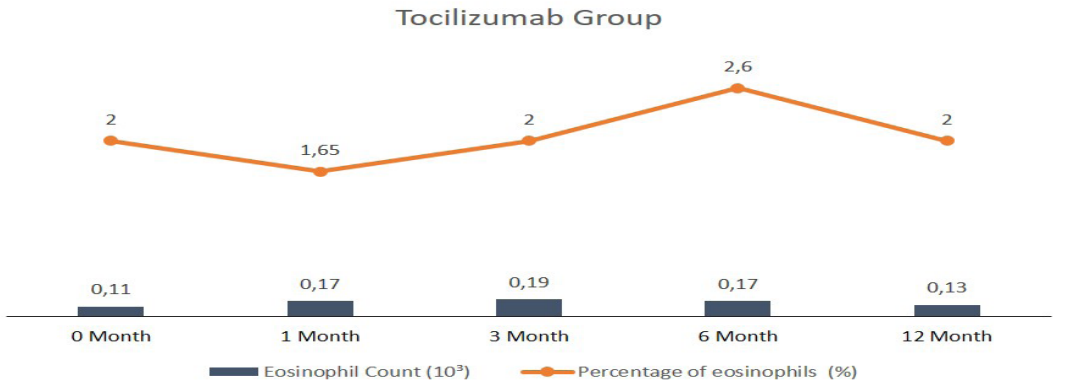

Figure 1. Eosinophil counts and percentages in the Tocilizumab group

which included relatively more active patients due to the inability to achieve remission with anti-TNF treatment, the initial DAS28 values were significantly higher than those in the DMARD group. However, with the successful suppression of disease activity by the 12th month, a contrasting scenario ensued. At the end of twelve months of treatment, complete remission (DAS28<2.6) was achieved in 47% of patients in this group, while others reached mild to moderate disease activity levels.

In this study, a significant increase in eosinophil counts was observed in the group receiving tocilizumab therapy at the 1st month, which persisted at the 3rd month but remained unchanged in subsequent follow-ups. Eosinophil percentages exhibited a significant increase at the 1st month, with no subsequent alterations. None of these patients developed a clinical picture that could be associated with eosinophilia. Given this context, it can be speculated that the increase in eosinophil counts may be related to a decrease in disease activity rather than developing as a side effect. However, due to limitations such as the small number of patients included in the study, the use of different treatments and combinations in the DMARD group, and the fact that some patients in the tocilizumab group had previously received anti-TNF treatment, it is not possible to reach a definitive conclusion. Nevertheless, these results underscore the necessity for more comprehensive studies on eosinophil counts in patients receiving tocilizumab therapy.

CONCLUSION

In recent literature, cases of tocilizumab-induced eosinophilia have been reported. Although the number of patients followed for one year in this study is limited, the results indicate a tendency for an early increase in eosinophil counts with tocilizumab treatment. Therefore, during treatment monitoring, especially in the early stages, attention should also be paid to eosinophil values. Patients should be informed about symptoms that may be associated with eosinophilia, and when such symptoms do not accompany the increase in eosinophil counts, it should be considered that this increase may be related to a decrease in disease activity.

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