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CLINICAL AND LABORATORY PREDICTORS OF THERAPEUTIC RESPONSE TO TOCILIZUMAB IN RHEUMATOID ARTHRITIS

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Summary

Introduction Biological disease-modifying antirheumatic drugs (bDMARDs), such as tocilizumab (TCZ), are essential for reducing disease activity in moderate to severe rheumatoid arthritis (RA). This study aims to identify clinical and laboratory predictors of a favorable response to TCZ, enabling personalized therapeutic strategies.

Material and methods A longitudinal clinical study in dependent samples included 133 bio-naïve patients (121 women, 12 men, mean age 49.87±13.31 years) with seropositive RA (radiological stages I-III) treated with TCZ and csDMARDs at the Timofei Moșneaga Republican Clinical Hospital. Clinical and laboratory parameters were monitored monthly over a six-month period. Statistical analysis was performed using Spearman's correlation and multiple regression. The Wilcoxon signed-rank test was applied to compare parameters before and after TCZ treatment.

Results Favorable response predictors included swollen joint counts (ρ=0.59, p<0.01), tender joint counts (ρ=0.40, p<0.01), C-reactive protein (ρ=0.46, p<0.01), ESR (ρ=0.25, p<0.01), platelet count (ρ=0.29, p<0.01), hemoglobin (ρ=-0.26, p<0.01), hematocrit (ρ=-0.23, p<0.01), and age (ρ=-0.49, p<0.01). Regression analysis confirmed the influence of swollen joint counts (ρ=0.30, p<0.001), age (ρ=-0.30, p<0.001), and C-reactive protein (ρ=0.18, p=0.016) on DAS28 reduction.

Conclusions Swollen and tender joint counts, C-reactive protein, and age are key independent predictors of therapeutic success with TCZ after six months of treatment.

Keywords Rheumatoid arthritis, bio-naïve, tocilizumab, predictors, markers.

PREDICTORII CLINICI ȘI DE LABORATOR AI RĂSPUNSULUI TERAPEUTIC LA TOCILIZUMAB ÎN ARTRITA REUMATOIDĂ

Introducere Medicamentele biologice antireumatice modificatoare de boală (bDMARDs), precum tocilizumab (TCZ), sunt esențiale pentru reducerea activității bolii în artrita reumatoidă (AR) moderată și severă. Studiul urmărește identificarea predictorilor clinici și de laborator ai unui răspuns favorabil la TCZ pentru optimizarea tratamentului personalizat.

Material și metode Studiul prospectiv a inclus 133 de pacienți bio-naivi (121 femei, 12 bărbați, vârsta medie 49,87±13,31 ani) cu AR seropozitivă (stadii radiologice I-III), tratați cu TCZ și csDMARDs la Spitalul Clinic Republican „Timofei Moșneaga". Parametrii clinici și de laborator au fost monitorizați lunar timp de 6 luni. Datele au fost analizate statistic prin corelații Spearman și regresie multiplă. Wilcoxon signed-rank test a fost utilizat pentru a compara parametrii înainte și după tratament.

Rezultate Parametrii asociați cu răspuns favorabil au inclus numărul articulațiilor tumefiate (ρ=0,59, p<0,01), numărul articulațiilor dureroase (ρ=0,40, p<0,01), proteina C reactivă (ρ=0,46, p<0,01), VSH (ρ=0,25, p<0,01), trombocitele (ρ=0,29, p<0,01), hemoglobina (ρ=-0,26, p<0,01), hematocritul (ρ=-0,23, p<0,01) și vârsta (ρ=-0,49, p<0,01). Regresia multiplă a confirmat influența numărului articulațiilor tumefiate (ρ=0,30, p<0,001), vârstei (ρ=-0,30, p<0,001) și proteinei C reactive (ρ=0,18, p=0,016) asupra reducerii scorului DAS28.

Concluzii Numărul articulațiilor tumefiate și dureroase, proteina C reactivă și vârsta sunt predictori esențiali ai succesului terapeutic cu TCZ după 6 luni de tratament.

Cuvinte-cheie Artrită reumatoidă, bio-naiv, tocilizumab, predictor, markeri.

INTRODUCTION

According to the Treat-to-Target (T2T) strategy, the primary objective in managing rheumatoid arthritis (RA) is to achieve and sustain remission or low disease activity (1). Biological disease-modifying antirheumatic drugs (bDMARDs), such as tocilizumab (TCZ), are essential in implementing this strategy in patients with moderate to severe RA. Despite their effectiveness, there is limited guidance on selecting the most appropriate bDMARD for initiating therapy in bio-naïve patients. Given that up to one-third of RA patients receiving tumor necrosis factor-alpha inhibitors (TNF-i) fail to achieve adequate clinical improvement, a personalized approach to bDMARD therapy may be warranted (2). Initiating treatment with the agent most likely to obtain a positive therapeutic response which could shorten the time to disease control, reduce healthcare costs, and prevent patient frustration – factors that may ultimately enhance treatment compliance. Evidence also suggests that bio-naïve patients may exhibit better responses to biologic therapies compared to those previously treated with biologics, although it remains uncertain whether this is attributable solely to their treatment-naïve status (3). To optimize treatment selection, it may be beneficial to identify clinical and laboratory parameters that predict a more favorable response to specific bDMARDs. This study aims to identify such predictive markers for tocilizumab, a humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor, in patients with seropositive RA.

MATERIAL AND METHODS

A longitudinal clinical study involving dependent samples was conducted on 133 biologic-naïve patients (121 women and 12 men) diagnosed with seropositive rheumatoid arthritis, according to the 2010 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria. All patients were receiving intravenous tocilizumab (TCZ) in accordance with standard treatment protocols, in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Tocilizumab was administered at a dose of 8 mg/kg every 4 weeks in 113 patients (85%), while the remaining 20 patients (15%) received 4 mg/kg at the same interval. In addition to TCZ, 115 patients (86%) were treated with methotrexate at weekly doses ranging from 10 to 12.5 mg, and 18 patients (14%) received leflunomide at a maintenance dose of 10–20 mg daily. Prior to initiating TCZ therapy, 101 patients (76%) were taking daily methylprednisolone at doses of 4–12 mg, while 32 patients (24%) did not require corticosteroids for symptom control. Corticosteroid dosages were individually tapered throughout the course of treatment. The mean age of the patients was 49.87 ± 13.31 years. Before initiating TCZ therapy, the mean disease activity, assessed using the Disease Activity Score in 28 joints with C-reactive protein (DAS28-CRP), was 6.12 ± 1.02, and the mean disease duration was 10.08 ± 6.9 years. Most patients had radiologically confirmed signs of disease, classified as Steinbrocker stage II in 64.66%, stage III in 30.83%, and stage I in 4.51%. Data from patients who discontinued or interrupted TCZ therapy – thereby deviating from the standard treatment regimen – as well as those who ceased csDMARD use, were excluded from the final analysis. To evaluate treatment efficacy, the following parameters were assessed prior to each TCZ administration (initially and then approximately once per month): tender joint count (TJC), swollen joint count (SJC), DAS28-CRP score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, hematocrit, red blood cell (RBC) count, absolute neutrophil count, absolute lymphocyte count, and platelet count.

Data were collected from the medical records of patients who received TCZ treatment at the Timofei Moșneaga Republican Clinical Hospital in Chișinău, Moldova, between February 2022 and July 2024, with informed patient consent. The compiled data were used to conduct statistical analyses aimed at identifying baseline clinical and laboratory parameters that could predict a favorable therapeutic response to TCZ. Spearman correlation coefficients were calculated to assess the relationship between individual parameters and the reduction in disease activity. Multiple regression analysis was conducted to determine independent predictors of treatment efficacy. The Wilcoxon signed-rank test was applied to compare clinical parameters before and after TCZ therapy. Disease activity was assessed using the composite score DAS28-CRP. To quantify changes in disease activity, the delta DAS28-CRP was calculated as the difference between the baseline DAS28-CRP score and the score recorded after six months of treatment. The multiple regression model used the following equation for the dependent variable DAS28-CRP: $z = \beta_0 + \beta_1X_1 + \beta_2X_2 + ... + \beta_kX_k$ where z – result of the equation, X_1-X_k – investigated predictors, β_0 – intercept, and β_1-β_k – regression coefficients. Probability of the multiple regression ($P = 1/(1 + e^{-z})$; e≈2.71828) and coefficient of multiple determination R^2 were calculated. The statistical analysis was performed using Statistica StatSoft 10, 95% CI, $p<0.05$.

This study did not require approval from an Ethics Committee because it adhered strictly to standard clinical protocols and guidelines outlined in the national clinical protocol *"Rheumatoid Arthritis in Adults"* of the Republic of Moldova. All procedures, including the administration of tocilizumab and csDMARDs, were carried out as part of routine medical practice and complied with national healthcare regulations under the mandatory health insurance program. Data were collected from patient records with full respect for anonymity and confidentiality. Informed consent was obtained from all participants for the use of their anonymized medical data for research purposes.

RESULTS

The EULAR response criteria for assessing treatment effectiveness in rheumatoid arthritis are based on changes in the DAS28 composite score after 3 to 6 months of therapy. A good response is defined as a reduction in DAS28 of more than 1.2, with a final score below 3. A moderate response corresponds to a reduction of 0.6 to 1.2, while a reduction of less than 0.6 indicates a non-response (4). According to these criteria, 49 patients (36.85%) were classified as good responders, 80 (60.15%) as moderate responders, and 4 (3.01%) as non-responders to tocilizumab therapy, which was added to their existing csDMARD and corticosteroid regimen.

Swollen joint count (SJC) showed a moderate positive correlation with the reduction in disease activity ($\rho = 0.59$, $p < 0.01$) (Fig. 1). Similarly, tender joint count (TJC) was positively correlated with disease activity reduction, though to a lesser extent ($\rho = 0.40$, $p < 0.01$) (Fig. 2). Age showed a moderate negative correlation with the reduction in disease activity ($\rho = –0.49$, $p < 0.01$). C-reactive protein (CRP) levels ($\rho = 0.46$, $p < 0.01$) (Fig. 3) and erythrocyte sedimentation rate (ESR) ($\rho = 0.25$, $p < 0.01$) were both positively associated with a reduction in disease activity. While the correlation with CRP was moderate, the correlation with ESR was weak. A moderate positive correlation was also observed between CRP and ESR ($r = 0.52$, $p < 0.01$). Baseline hemoglobin ($\rho = –0.26$, $p < 0.01$) and hematocrit ($\rho = –0.23$, $p < 0.01$) levels before initiating TCZ therapy were inversely correlated with the degree of DAS28 reduction. An increase in hemoglobin levels was noted over the course of treatment (Fig. 4). Platelet counts, although within normal ranges, showed a weak but statisti-

cally significant positive correlation with the reduction in disease activity ($\rho = 0.29$, $p < 0.01$) (Fig. 5). In contrast, red blood cell counts, absolute neutrophil and lymphocyte counts, and disease duration did not demonstrate any significant correlation with changes in disease activity.

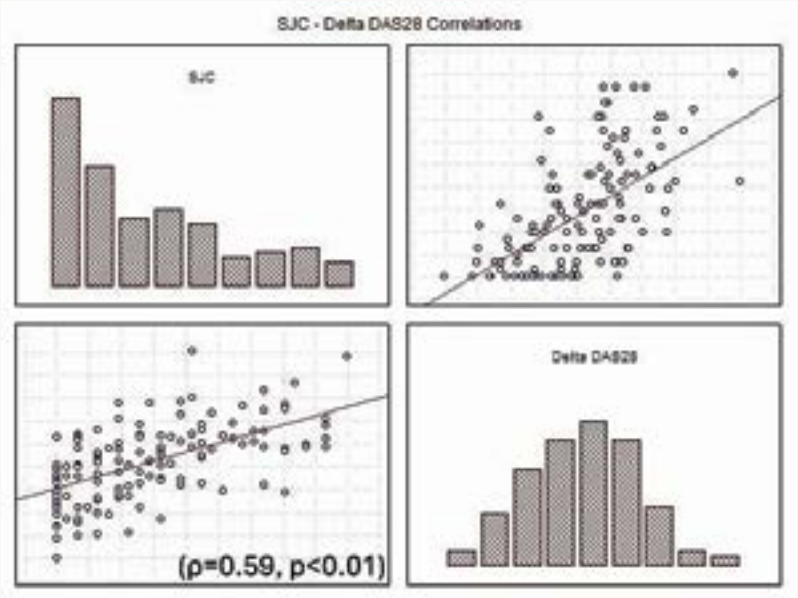

Figure 1. Swollen joint count (SJC) upon the start of tocilizumab therapy correlated with reduction in DAS28-CRP score after a 6-month treatment (scatterplot).

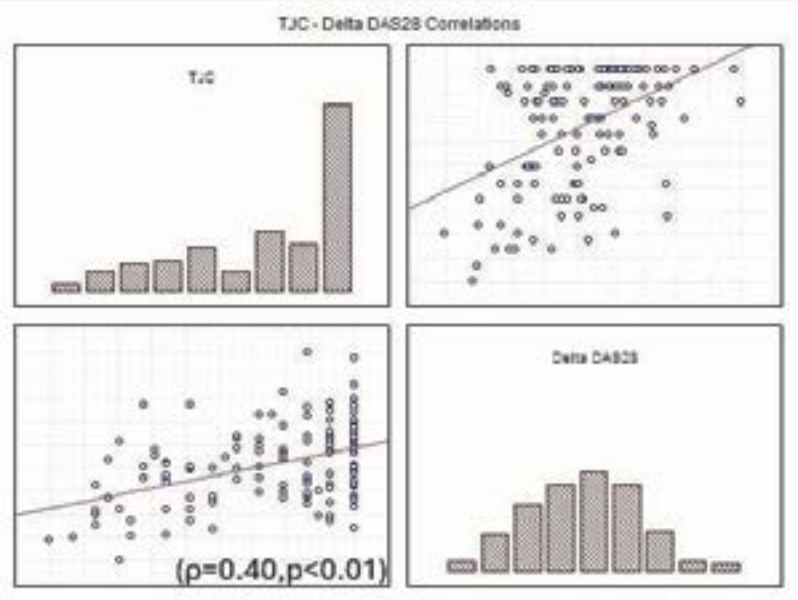

Figure 2. Tender joint count (TJC) upon the start of tocilizumab therapy correlated with reduction in DAS28-CRP score after 6-month treatment (scatterplot).

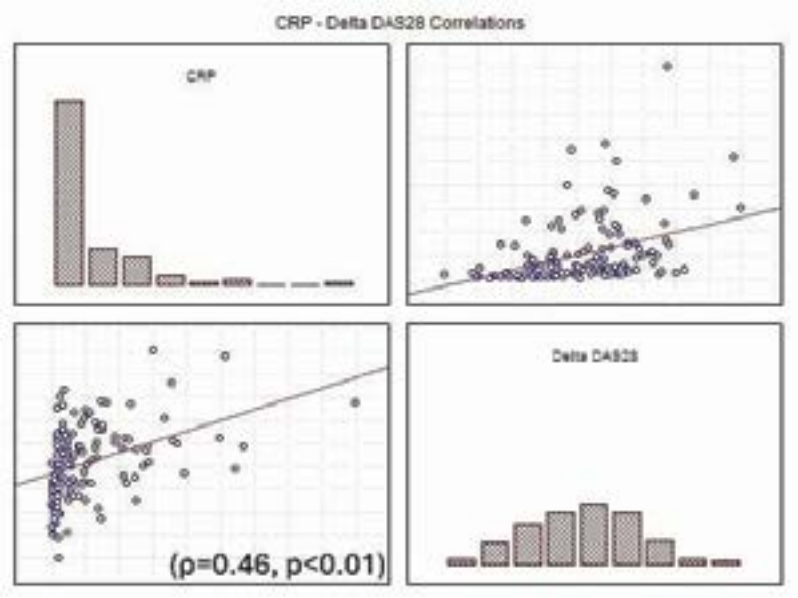

Figure 3. C-reactive protein levels upon the start of tocilizumab therapy correlated with reduction in DAS28-CRP score after 6-month treatment (scatterplot).

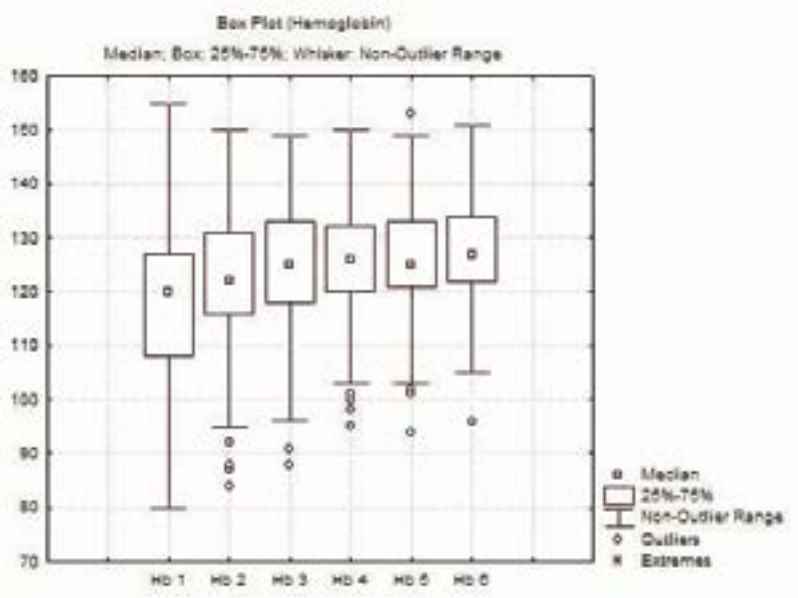

Figure 4. Hemoglobin levels assessed monthly over the 6-month treatment period (box and whisker plot).

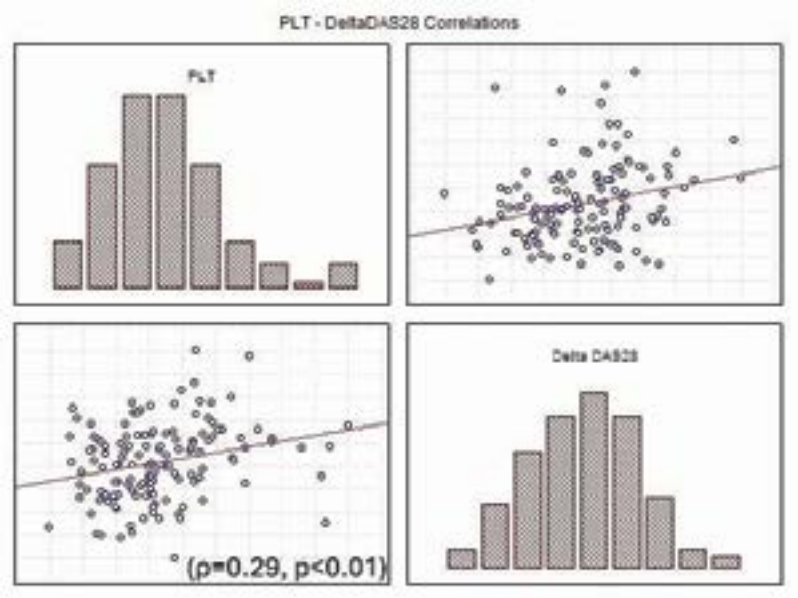

Figure 5. Platelet count upon the start of tocilizumab therapy correlated with reduction in DAS28-CRP score after 6-month treatment (scatterplot).

A multiple regression analysis was performed to evaluate the combined effect of various factors on the dependent variable ΔDAS28. The resulting equation was as follows:

$$z = 2.346 - 0.3X_1 + 0.085X_2 + 0.145X_3 + 0.240X_4 + 0.30X_5 - 0.25X_6 + 0.246X_7 - 0.08X_8 - 0.01X_9 + 0.020X_{10} + 0.038X_{11} + 0.001X_{12}$$

where X_1 – patient age; X_2 – erythrocyte sedimentation rate; X_3 – C-reactive protein levels; X_4 – tender joint count; X_5 – swollen joint count; X_6-hemoglobin level; X_7 – hematocrit; X_8 – red blood cell count; X_9 – neutrophil count; X_{10}- lymphocyte count; X_{11} – duration of disease; X_{12} – platelet count.

The multiple regression model was statistically significant, adjusted R^2 = 0.4863 ($p<0.001$). The calculated probability of multiple regression was high (P=94%).

Regression analysis determined SJC (β=0.30, $p<0.001$), TJC (β=0.24, p=0.0012) and age (β=-0.30, $p<0.001$) as significant predictors. Neither CRP nor ESR showed statistically significant beta coefficients in the model when both were included ($p > 0.05$). However, when CRP was excluded, ESR became a significant predictor (β = 0.16, p = 0.028), and when ESR was excluded, CRP showed a significant effect (β = 0.18, p = 0.016). Hemoglobin level, hematocrit, platelet count, red blood cell count, and absolute neutrophil and lymphocyte counts were not statistically significant predictors ($p > 0.05$).

The tables below present the pre- and post-treatment values of the analyzed clinical (Tab. 1) and laboratory (Tab. 2) parameters, along with the median change in each parameter following tocilizumab treatment and the statistical significance of these changes, as determined by the Wilcoxon signed-rank test.

Table 1. Clinical features assessed at the initiation of tocilizumab therapy.

Clinical parameters	Mean before TCZ	Mean after 6 months of treatment	Median of change after 6 months of treatment	Significance level calculated by Wilcoxon signed-rank test (p)
TJC	21.1±7.3	8.1±5.3	- 13.0	<0.001
SJC	8.8±7.6	1.4±2.4	- 6.0	<0.001
DAS28-CRP	6.1±1.02	3.5±0.8	- 2.64	<0.001
Note: TJC, tender joint count; SJC, swollen joint count. DAS28-CRP, Disease Activity Score in 28 joints with C-reactive protein.				

Table 2. Laboratory findings assessed at the initiation of tocilizumab therapy.

Laboratory parameters	Mean before TCZ	Mean after 6 months of treatment	Median of change after 6 months of treatment	Significance level calculated by Wilcoxon signed-rank test (p)
ESR (mm/hour)	25.7±14.9	6.9±6.6	- 15.0	<0.001
CRP (mg/L)	19.1±25.0	2.2±2.9	- 7.1	<0.001
Hb (g/L)	118.2±14.5	127.8±9.8	9.0	<0.001
Hct (%)	36.43±4.22	38.36±2.86	1.5	<0.001
RBC ($\times 10^6/\mu L$)	4.16±0.42	4.17±0.29	-0.16	0.524
NEU ($10^3/\mu l$)	4.25±2.1	4.4±1.3	0.67	0.106
LYM ($10^3/\mu l$)	2.1±0.8	5.5±5.0	3.85	<0.001
PLT ($10^3/\mu l$)	311.8±91.5	208.5±53.0	-97.0	<0.001
Note: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, Hemoglobin; Hct, hematocrit; RBC, red blood cell count; NEU, absolute neutrophil count; LYM, absolute lymphocyte count; PLT, platelet count.				

DISCUSSIONS

In previous studies, rheumatoid factor, platelet count, hemoglobin levels, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) have been identified as potential predictors of a more favorable response to tocilizumab compared to other bDMARDs (5, 6). In the present sample, factors associated with a greater reduction in disease activity included elevated CRP and ESR, higher platelet counts, lower hemoglobin and hematocrit levels, younger age, and increased swollen and tender joint counts.

C-reactive protein is an acute-phase reactant produced by hepatocytes in response to stimulation by pro-inflammatory cytokines, particularly interleukin-6 (IL-6), whose activity is inhibited by TCZ (7). Previous studies suggest that in certain cases of RA, specific cytokines may play a more dominant role, rendering bDMARDs targeting less involved pathways less effective (2). It has been proposed that CRP could serve as a readily accessible, indirect marker of IL-6-driven disease, with higher baseline CRP levels potentially indicating greater responsiveness to IL-6 blockade. However, CRP appears to be an

unreliable standalone predictor of therapeutic efficacy, as reductions in CRP levels do not consistently correspond with clinical improvement (8, 9).

In contrast to CRP, ESR is also likely influenced by RF and other immunoglobulins (10). A 2022 study further suggests that ESR may serve as a predictor of tocilizumab efficacy in slowing the radiological progression of RA (11). However, due to its low specificity, ESR should be considered a supportive indicator of disease activity – and by extension, a potential predictor of treatment response – only when interpreted alongside more specific biomarkers and clinical findings.

Platelet counts are elevated by IL-6 through increased megakaryocyte differentiation and high thrombopoietin expression (12). It has been hypothesized that elevated platelet counts may characterize RA cases in which IL-6-driven inflammation predominates. A 2017 study used platelet counts, along with hemoglobin, AST, and ALT levels, to develop a scoring system for comparing the efficacy of TCZ and TNF-i therapies (6). The present findings align with the notion that higher platelet counts may be associated with a more favorable response to TCZ.

In this patient cohort, pre-treatment hemoglobin levels showed an inverse correlation with treatment efficacy. The gradual increase in hemoglobin observed during therapy (Figure 4) suggests that systemic inflammation was likely a major contributing factor to anemia at the tocilizumab treatment initiation. Prior to therapy, 62 patients (46%), all of whom were women, were found to be anemic – 34 with moderate and 28 with mild anemia based on hemoglobin levels. As inflammation subsided, hemoglobin levels rose, and by six months, anemia was identified in only 17 patients (13%) – 4 with moderate and 13 with mild anemia.

Although the literature supports the beneficial effect of TCZ on hemoglobin levels in patients with RA (13), this study lacks data on baseline iron status. It remains unclear whether any patients received concurrent treatment for iron deficiency anemia, making it difficult to determine the relative impact of iron deficiency versus RA-associated chronic inflammation on hemoglobin levels. Nevertheless, a 2013 study also reported that tocilizumab was more effective in improving anemia than TNF-α inhibitors, attributing this effect to reduced hepcidin production following IL-6 inhibition (14).

In the present study sample, younger patients tended to show a greater reduction in disease activity, a finding consistent with previous research (15). This may be partly due to a shorter disease duration, as biological therapy was initiated sooner after diagnosis in younger patients compared to older ones. Consequently, younger individuals often exhibit fewer morphological changes, and the associated cyto-molecular processes may be less established. A similar rationale has been proposed in discussions regarding whether bio-naïve patients respond more favorably to biologics, as they are typically younger, have a shorter disease course, and exhibit less advanced pathological changes. However, in this sample, disease duration was not a significant predictor of TCZ treatment efficacy.

In the study sample, both tender and swollen joint counts showed a correlation with tocilizumab efficacy. Among them, the swollen joint count was the more significant and specific predictor of therapeutic success, a finding supported by previous studies as well (16). One possible explanation for the superior predictive value of SJC is that tenderness may be reported in joints affected by other conditions, such as osteoarthritis, making it a less specific marker for RA activity. In contrast, joint swelling can be more objectively assessed by the clinician, thereby offering greater diagnostic specificity.

Multiple recent studies contributed to the individualization of treatment by comparing the efficacy of various biologic agents and exploring cyto-molecular characteristics of RA that may serve as predictors of therapeutic response (17). Notably, elevated levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) have been associated with a poor response to tocilizumab (18). At the same time, the combination of histopathological classification and genetic analysis appears to offer promising results in identifying RA subtypes more likely to respond to specific therapies, thus guiding the choice of therapies (19).

This study has several limitations. Firstly, the relatively small sample size limited the ability to thoroughly analyze less typical presentations of RA (e.g., age <30, disease duration >25 years). Secondly, the medical charts lacked detailed information on investigations and treatments unrelated to RA management, which prevented conclusions regarding certain findings – such as potential causes of the observed changes in hemoglobin levels. Thirdly, the data reflected outcomes only at the end of a limited follow-up period, making it uncertain whether the identified predictors remain valid for maintaining low disease activity beyond the 6-month period.

CONCLUSIONS

1. A greater reduction in disease activity following tocilizumab treatment added to background therapy was positively associated with higher swollen and tender joint counts, elevated C-reactive protein (CRP) levels, increased erythrocyte sedimentation rate (ESR), and elevated platelet counts.
2. Hemoglobin and hematocrit levels were negatively correlated with the reduction in disease activity.
3. Swollen and tender joint counts, as well as age, were identified as independent predictors of improved therapeutic response to tocilizumab.
4. These findings indicate that bio-naïve, seropositive rheumatoid arthritis patients who are younger, exhibit high disease activity, and have a greater number of affected joints are more likely to achieve a favorable response to tocilizumab after six months of treatment.

CONFLICT OF INTEREST

The authors of the article deny the existence of any conflict of interest in the publication of this research.

ETHICS APPROVAL

The study was approved by the Research Ethics Committee of the Nicolae Testemițanu State University of Medicine and Pharmacy (Decision no. 21 of 21.12.2019).

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