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Evaluation of Anemia in Rheumatoid Arthritis Patients and the Effect of Biological Therapy On Anemia of Chronic Disease

Romatoid Artrit Hastalarında Aneminin Değerlendirilmesi ve Biyolojik Tedavinin Kronik Hastalık Anemisi Üzerine Etkisi

ABSTRACT

Objective:

The aim of the study was to evaluate the frequency of anemia in patients with rheumatoid arthritis (RA), observe the change of anemia with biological disease-modifying anti-rheumatic drugs (bDMARDs) treatment and examine factors associated with anemia change before and after treatment.

Material and Methods:

The frequency of anemia before treatment was evaluated in 401 patients who received bDMARD therapy for 1 year. Patients' hemoglobin (HB), ferritin, transferrin saturation, mean corpuscular volume (MCV), hematocrit (HCT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels and disease activity score (DAS)28 were recorded. The data obtained before and 1 year after the treatment of patients with anemia of chronic disease (ACD) were compared and anemia evaluations of the patients were made.

Results:

Anemia was detected in 45.9% of 401 patients. Iron deficiency anemia (IDA) was observed in 58.2% of the 184 patients with anemia, ACD and ACD/IDA (mixed type) was observed in 31.5%. While ESR, CRP and DAS28 values decreased in the first year of bDMARD treatment, HB levels increased. When the increase in hemoglobin levels and decreased DAS28 were compared between adalimumab and sertolizumab, no significant difference was found. High basal ferritin and lower HB levels were found to be factors affecting HB change before and after treatment.

Conclusions:

While disease activity is controlled with bDMARD treatment, an increase in HB levels is also observed. ACD improves with disease treatment. High basal ferritin and lower HB levels were the most important factors associated with HB change.

Key Words:

Rheumatoid arthritis, Anemia, Anemia of chronic disease, Biological therapy

ÖZ

Amaç:

Bu çalışmanın amacı, romatoid artritli (RA) hastalarda anemi sıklığını değerlendirmek, biyolojik hastalık modifiye edici anti-romatizmal ilaçlar (bDMARD) tedavisi ile anemideki değişimi gözlemlemek ve tedavi öncesi ve sonrası anemi değişimi ile ilişkili faktörleri incelemektir.

Gereç ve Yöntemler:

Tedavi öncesi anemi sıklığı 1 yıl bDMARD tedavisi alan 401 hastada değerlendirildi. Hastaların hemoglobin (HB), ferritin, transferrin satürasyonu, ortalama eritrosit hacmi (MCV), hematokrit (HCT), eritrosit sedimantasyon hızı (ESH), C-reaktif protein (CRP) düzeyleri ve hastalık aktivite skoru (DAS) 28 kaydedildi. Kronik hastalık anemisi (KHA) olan hastaların tedavi öncesi ve tedaviden 1 yıl sonraki verileri karşılaştırıldı ve hastaların anemi değerlendirmeleri yapıldı.

Bulgular:

Dört yüz bir hastanın %45,9'unda anemi saptandı. Anemisi olan 184 hastanın %58,2'sinde demir eksikliği anemisi (DEA), %31,5'inde KHA ve KHA/DEA (mikst tip) görüldü. BDMARD tedavisinin ilk yılında ESH, CRP ve DAS28 değerleri düşerken, HB seviyeleri yükseldi. Adalimumab ve sertolizumab arasında hemoglobin düzeylerindeki artış ve DAS28'deki azalma karşılaştırıldığında anlamlı bir fark bulunmadı. Yüksek bazal ferritin ve düşük HB seviyeleri tedavi öncesi ve sonrası HB değişimini etkileyen faktörler olarak bulundu.

Sonuçlar:

BDMARD tedavisi ile hastalık aktivitesi kontrol altına alınırken HB düzeylerinde de artış gözlenmektedir. KHA hastalık tedavisi ile düzelir. Yüksek bazal ferritin ve düşük HB seviyeleri, HB değişikliği ile ilişkili en önemli faktörlerdi.

Anahtar Sözcükler:

Romatoid artrit, Anemi, Kronik hastalık anemisi, Biyolojik tedavi

INTRODUCTION

Anemia is the most common hematological disorder. Anemia of chronic disease (ACD) and anemia of iron deficiency are the most common types of anemia. ACD is seen in malignancies, chronic infections, autoimmune diseases, chronic kidney disease and chronic rejection after organ transplant (1).

RA is a chronic, inflammatory, autoimmune disease. In addition to synovial inflammation, extra-articular manifestations such as ACD are observed in rheumatoid arthritis. Proinflammatory cytokines are involved in the pathogenesis of both RA and ACD (2). CRP, a clinical marker of inflammation, has been associated with elevated IL 6 as an inflammatory cytokine (3). The DAS28, which contains information on tender joints, swollen joints, and acute phase reactants, is used to assess disease activation in patients with rheumatoid arthritis (4). Due to the presence of inflammatory cytokines in the pathogenesis, the aim of the treatment is to suppress inflammation. In patients who are unresponsive to conventional synthetic (cs)DMARD therapy, targeted synthetic (ts)DMARDs and bDMARD therapy are used (5). These treatments include TNF inhibitors, IL-6 receptor antagonist, T cell co-stimulatory blocker and B cell specific depletor (6). The demonstration of an increase in inflammatory cytokines in the pathogenesis of ACD suggests that HB levels will increase with these treatments. As a matter of fact, there are studies focusing on the treatment and HB levels in chronic diseases such as Castleman's disease, RA and ankylosing spondylitis (7, 8). The aim of our study was to evaluate the frequency of anemia in RA patients before biologic therapy, observe the change of ACD with bDMARDs treatment and and examine factors associated with anemia change before and after treatment.

MATERIALS and METHODS

Study design

The study population was selected from patients diagnosed with RA who applied to our rheumatology outpatient clinic between December 2015 and December 2022. The study was conducted in accordance with research and publication ethics (9).The study protocol was approved by Cukurova University Faculty of Medicine Ethics Committee (Date:6.01.2023, Reference number: 129/37). Patients diagnosed in accordance with ACR 2010 criteria were included in the study (10). Patients were reviewed retrospectively from the hospital system, and those who received biologic therapy regularly for 1 year were evaluated. Patients were grouped as those with and without anemia at the time of initiation of biological therapy. Anemia was defined as those below 13 g/dl in men and 12 g/dl in women. Transferrin saturation, ferritin, b12, folate, mean corpuscular volume (MCV) were measured to evaluate the patients with anemia in terms of iron deficiency, b12 deficiency and ACD. Patients with a transferrin saturation greater than 16% and a ferritin level above 100 ng/ml were classified as ACD. Patients with ferritin between 30-100 ng/ml, TS <16%, and high CRP were classified to have

iron deficiency and ACD. With the planned algorithm, the patients were evaluated in terms of anemia and disease activation before bDMARDs. Flowchart of patients' selection process was shown in Figure 1.

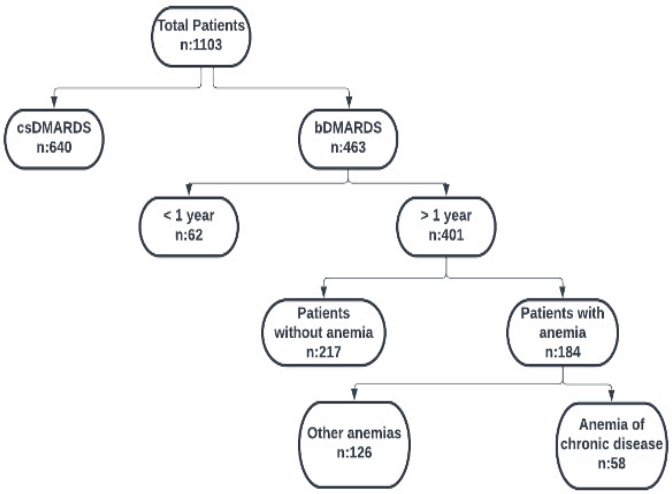

Figure 1: Flowchart of patients' selection process
csDMARDS: conventional synthetic disease-modifying anti-rheumatic drugs bDMARDS: biological disease-modifying anti-rheumatic drugs

Patients with ACD were evaluated for disease status with hemoglobin, hematocrit, DAS28, ESR, and CRP before bDMARD and 1 year after treatment. The relationship between treatment and disease activation status and hemoglobin was examined. Patients under the age of 18, pregnant women, patients with kidney failure, liver failure and cancer diagnosis were excluded from the study.

Statistical Analysis

Categorical variables were explained as numbers and percentages, whereas continuous variables were expressed as mean and standard deviation. The normality of distribution for continuous variables was confirmed by the Shapiro Wilk test. Depending on whether the statistical hypotheses were met, samples t-test or Wilcoxon Signed Rank test was used. The indicated tests were used to evaluate the comparison of pre- and post-treatment variables. The correlations between the measurements were evaluated with the Pearson coefficient of correlation. Determinants of hb change were analyzed by linear regression analysis. IBM SPSS Statistics Version 20.0 statistical software package was used for all analyzes. Statistical significance level was determined as p <0.05 for all tests with IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

RESULTS

Four hundred and one patients with a diagnosis of RA who were found to be receiving regular biologic therapy for 1 year were included in the study. 352 (87.8%) of the patients were women. The average age of women was 51.92±14.39. Anemia was observed in 45.9% (184 patients) of these patients. 58.2% of the patients with anemia (107 patients) had IDA, 31.5% of the patients had ACD or coexistence of chronic disease and iron deficiency (49 patients had anemia of chronic disease, 9 patients had mixed anemia). Thalassemia minor-intermedia, b12/iron deficiency coexistence, anemia of other chronic diseases, and b12 deficiency anemia were observed in 11, 5, 2, and 1 patients respectively. Patients with RA and ACD are shown in Table I.

Table I: Characteristics of RA patients with anemia of chronic disease

Total number of patients	58
Gender (Female/male)	47/11
Age (years, mean±SD)	53.7±16
Anemia of chronic disease, n(%)	49
Anemia of chronic disease and anemia of iron deficiency, n(%)	9
Number of seropositive patients, n(%)	34(64.2)
Disease duration (year, mean±SD)	12.86±9.69
Time between biological therapy and diagnosis(year, mean±SD)	9.8±9.3
Biological treatments	58
Adalimumab, % (n) Certolizumab, %(n) Etanercept, %(n) Tocilizumab, %(n) Abatacept, %(n) Golimumab, %(n) Tofacitinib, %(n)	34.5 (20) 32.8(19) 10.3(6) 8.6(5) 6.9(4) 5.2(3) 1.7(1)
Comorbid diseases	
Diabetes mellitus, % (n) Hypertension, %(n) Coronary artery disease, %(n) Chronic obstructive pulmonary disease, %(n) Osteoporosis, %(n)	6.9(4) 34.5(20) 3.4(2) 6.9(4) 22.4(13)

Anemia disappeared in 55.2% of the patients after 1 year of treatment. The increase in HB of the patients, the decrease in the acute phase reactants and DAS28 levels are shown in Table II, and it was seen that the treatment had a statistically significant effect on HB (p <0.001).

Table II. Changes before and after treatment

	Before treatment			After treatment			p value
	Mean±SD	Median	Min-max	Mean±SD	Median	Min-max	
HB	11±0.86	11.1	8.5-12.8	12.1±1.03	12.3	10.2-14.7	<0.001
HCT	33.4±2.6	33.7	27-38.8	36.5±2.83	35.7	31.5-43	<0.001
MCV	82.5±6.7	81.7	65.7-98.5	83.2±5.9	83.6	70-98.8	0.26
ESR	55.6±24	55.5	4-100	29.3±18.7	28.5	2-88	<0.001
CRP	59.9±56.2	41.7	7-360	13±16.1	7	1-76	<0.001
DAS28	7.23±0.59	7.36	5.8-8.3	4±0.91	3.9	2.5-7	<0.001

HB: Hemoglobin, HCT: Hematocrit , MCV: Mean corpuscular volume , ESH: Erythrocyte sedimentation rate, CRP: C-reactive protein and DAS28: Disease activity score 28

As seen in Table I, the most commonly preferred biologic treatments were adalimumab and certolizumab. It was observed that the patient groups receiving adalimumab and certolizumab had similar efficacy when the DAS28 decrease and HB change were evaluated (Table III).

Table III. Evaluation of adalimumab and certolizumab therapy

	Adalimumab	Certolizumab	p value
Number of patients	20	19	
Decrease in DAS28 with treatment(Mean±SD)	3.22±0.96	3.24±0.87	0.93
Hb change with treatment (Mean±SD)	1.41±0.87	1.18±0.62	0.37

DAS28: Disease activity score 28, Hb: Hemoglobin

According to the results of the correlation analysis, no correlation was found between HB change and age, disease duration (years), bDMARD onset time, basal ESR, CRP, DAS-28, HCT, MCV, transferrin saturation ($p<0.05$). There was a significant positive correlation between HB change and basal ferritin level after treatment, and a significant negative correlation with basal HB ($p<0.001$ $r=0.458$; $p=0001$ $r= -0.411$ respectively).
Finally, the factors affecting hemoglobin levels were evaluated by lineer regression analysis. Pretreatment CRP, pretreatment HB, DAS-28, hct, ferritin and ESR were included in the logistic regression analysis.By stepwise method (forward selection) ferritin level and basal HB levels were found to be significant which are shown in Table IV.

Table IV: Factors affecting the change in hemoglobin level

	Beta	Std. error	p value
Ferritin	0.002	0.001	0.002
Hb before biologic therapy	-.374	0.137	0.008
Hb change with treatment (Mean±SD)	1.41±0.87	1.18±0.62	0.37

HB: Hemoglobin

DISCUSSION

The presence of anemia in RA patients has been reported between 30-60% (11, 12). In our study, the frequency of anemia was high with a rate of 45.9%. Although anemia cases in RA show iron deficiency due to gastrointestinal bleeding related to NSAID use, it has been reported in the literature that 60% of anemia is ACD in this patient group (13). It was stated in the literature that the most common anemia in RA patients was ACD. Neverthless, IDA was the most common type in our study. Iron deficiency and IDA are quite common in women (14). In our study, 352 (87.8%) of 401 patients were women. The frequent occurrence of IDA can be associated with the majority of women. ACD was seen in 31.5% of our patients with anemia. The incidence of thalassemia minor-intermedia has increased in the region of our study. In our study, anemia of 11 patients was associated with thalassemia (15).
In the study conducted by Padula et al., the change in HB levels with treatment was examined, but the study did not focus on patients with ACD (16). In this study, the change in HB and CRP with biological treatments was examined. The efficacy difference between treatments on anemia was investigated. In our study, we focused on patients with ACD, because HB levels are not expected to increase with RA treatment of patients with iron deficiency or b12 deficiency anemia. Hb increase with treatment and decrease in CRP levels with DAS 28 were found to be significant ($p <0,001$). Increase in HB levels with treatment is associated with improvement in disease level. Studies have shown that IL6 inhibitor and TNF alpha inhibitor therapy increase hemoglobin levels in patients with RA (17). In this study, we showed that hb levels increased with bDMARD treatment, as in the studies in the literature. In this patient group, the most common antiTNF treatments were adalimumab and certolizumab. While disease activity decreased with these treatments, HB level increased. Similar efficacy was seen in the two antiTNF groups.
There are studies on ACD in the literature. However, HB change was more pronounced in patients with low pre-treatment hb levels and high ferritin levels. The studies did not focus on the factors affecting the HB change. Besides being an acute phase reactant of ferritin, it also takes part in iron metabolism. The relationship was found between increased ferritin and DAS 28 in RA patients (18). In the study conducted by Vanarsa et al. in patients with systemic lupus erythematosus, a relationship was found between increased ferritin levels and inflammatory cytokines, and anemia (19). TNF-alpha and interleukin 1, which are proinflammatory cytokines involved in the pathogenesis of RA, are known to stimulate ferritin expression. Based on above mentioned data, ferritin may be more successful than other acute phase reactants (ESR, CRP) in predicting the change of ACD in RA patients with DMARD treatment.
Our study has some limitations. Each bDMARD treatment could not be compared due to the small number of ACD. It is also a retrospective study.

CONCLUSION

Considering the strengths of our study, as far as we know, it is the first study to examine the factors affecting HB change with bDMARD treatment in RA patients. In addition, patients with other anemia etiologies were separated and a patient group with CDA was formed and the analyses continued on that group. In conclusıon, we think that by evaluating the factors affecting the Hb change in rheumatoid arthritis patients, we have contributed to the science about anemia and its treatment in this patient group.

Ethics Committee Approval:
This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by Cukurova University Faculty of Medicine Ethics Committee (Date:6.01.2023, Reference number: 129/37).

Author Contributions:
Concept -G.V.; Design -G.V.,İ.T.S.Ö.; Supervision -G.V.,İ.T.,İ.Ü.,S.Ö.; Resources -G.V.,İ.T.,S.Ö.; Data Collection and/or Processing – G.V., Z.T.,S.Ö; Analysis and/ or Interpretation – G.V.,İ.T.,Z.T.,S.Ö.,İ.Ü Literature Search - G.V.,İ.T.,Z.T.,S.Ö.,İ.Ü.; Writing Manuscript – G.V.,İ.T.,Z.T.,İ.Ü.; Critical Review – İ.T.,Z.T.,S.Ö.

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

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