The Egyptian Journal of Hospital Medicine (January2023) Vol. 90 (2), Page 3182-3188

Biological Therapy and Hematological Parameters in Rheumatoid Arthritis Patients

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder. One of the primary pro-inflammatory cytokines that involved in joint damage is tumor necrosis factor alpha (TNFα). RA is treated using variety of disease modifying anti-rheumatic drugs (DMARDs). The conventional-synthetic disease modifying anti-rheumatic drugs (cs-DMARDs) are corner stone in the treatment of RA patients, however they have limited efficacy in induction of remission.

Objective: This study aims to assess the hematological impact of biological therapy in Rheumatoid arthritis patients in comparison to conventional synthetic disease modifying anti rheumatic drugs.

Patients and methods: On the other hand, the biological therapies are potent and strong, highly targeted therapy that successfully induce remission. This study compares the hematological effects of biological therapy and conventional synthetic disease-modifying anti-rheumatic medications in patients with rheumatoid arthritis.

Results: Our results showed that patients on biological therapy had lower total leucocytic and neutrophils count with higher lymphocyte count. As well as, they showed statistically highly significant lower RDW with statistically significant higher hematocrit value, Hb concentration, RBCs count and MCV. Finally, we found that there was a statistically significant correlation between the duration of biological therapy and the RDW and MPV, and a highly statistically significant correlation with the values of Hb concentration, total platelet count and their related ratios.

Conclusion: Biological therapy had obvious effects on hematological parameters, and these effects were related partially to the potent nature of these group of drugs and partially related to the nature of each therapeutic agent. Additionally, these hematological effects were in strong correlation with the duration of biological use.

Keywords: RA, Biological therapy, cs-DMARDs, RBC, Hb, PLT.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder [1]. It is accompanied by progressive articular cartilage and bone erosion as well as synovial hyperplasia with pannus growth [2]. One of the primary pro-inflammatory cytokines involved in joint damage is tumor necrosis factor alpha (TNF-α) [3].

The main target in RA treatment is to reduce inflammation and obtain remission in order to stop or slow down bones and joints erosions. This was accomplished by utilizing various disease-modifying anti-rheumatic drugs (DMARDs) [4]. The cornerstone in treatment of RA is the use of conventional-synthetic disease-modifying anti-rheumatic drugs (cs-DMARDs), such as methotrexate, steroids and hydroxychloroquine. These drugs have the ability to reduce inflammation but have limited ability to induce remission [5]. The biological therapy, including anti-TNF agents, targets specific soluble or cell-surface molecules [4, 6, 7].

Several clinical trials revealed that biological therapy has a favorable impact on the treatment of RA [8]. Red blood cells (RBC) and related metrics like hemoglobin contents (Hb) and red blood cell distribution width (RDW) have been postulated as inflammatory biomarkers for predicting the severity of some autoimmune illnesses [9].

Recent researches have shown that platelets (PLT) play a crucial role in inflammatory responses [10].

The diagnostic utility of RBCs and PLTs indices and associated parameters in RA patients, however, is little understood. A few researches evaluated the relationship between PLT, RBC, Hb, red blood cells-platelet ratio (RPR), and the hemoglobin-platelet ratio (HPR) and RA disease activity. There is growing evidence that metrics like RDW and MPV, as well as the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and others have been considered to be accurate, reliable inflammatory biomarkers in autoimmune illnesses [11, 12]. Moreover, the therapeutic use of biological treatment may result in serious hematological abnormalities. According to certain studies, anti-TNFα medications can result in thrombocytopenia, neutropenia, or eosinophilia, as well as aplastic anemia [13].

TNFα is stated as a bifunctional hematopoiesis regulator. While prolonged exposure to it causes a decrease in early myeloid progenitors, acute short-term upregulation induces growth of immature immune cells [14, 15].

This study compares the hematological effects of biological therapy and conventional synthetic disease-modifying anti-rheumatic medications in patients with rheumatoid arthritis.

Received: 12/10/2022
Accepted: 15/12/2022

PATIENTS AND METHODS

Study design and setting: A cross-sectional study was conducted at the outpatient clinics of Ain Shams University-hospitals over 6 months.

Participants: This study included convenience sample of 141 rheumatoid patients that over a six-month period recruited from the outpatient clinics of the Ain Shams University hospitals.

Patients with RA who met the 2010 American College of Rheumatology ACR/European League Against Rheumatism categorization criteria for RA [16], were eligible for inclusion in this study [16].

The included group of RA must include patients receiving biological therapy and other receiving conventional non-biological therapy (cs-DMARDs) but they were randomly recruited. Individuals with other rheumatological disorders were disqualified from this research, as well as who suffered from hematologic diseases, malignancy, chronic renal or hepatic disease and other autoimmune diseases, patients who received pulse steroid of month duration before sampling, acute illnesses or infection, or a history of blood transfusions within the three months before to sample.

Patients were divided into two separate groups; Group I (N=49): who were on conventional non-biological therapy (cs-DMARDs), and Group II (N= 92): how received biological therapy. At study entry, participants continued their treatment therapy including conventional and biological therapy.

All patients underwent:

A-Full medical history taking with particular concern about onset and disease duration and drug history including the type, dose and duration.

B- Clinical assessment including general and musculoskeletal examination. **C-** Blood sample: 5 cm blood was drawn directly into buffered sodium citrate solutions, mixed right away, and processed in less than two hours. The following parameters were detected; **(1)** Complete blood count and different blood indices were estimated using Coulter counter, including (RBCs, Platelet, WBCs, neutrophil, lymphocyte, Hb, HCT, MCV, MCH, RDW, MPV and PDW), **(2)** The ABX Pentra 60 hematological analyzer was used to assess hematological variables (Horiba Medical, Irvine, CA, USA). Hb/PLT ratio, RDW/PLT ratio, RBCs/PLT ratio, Hb/RDW ratio, NLR, and PLR were calculated.

Ethical approval:

All participants received written consent and information about the study's goals prior to enrolment. The Research Ethical Committee Ain Shams University granted its ethical approval (FMASU R 92/2022). In accordance with the updated Helsinki declaration of biomedical ethics, confidentiality will be protected when handling the data.

Statistical analysis

The 28th release of IBM Corp.'s SPSS program, which was released in 2021, was used to evaluate the acquired data. Version 28.0 of IBM SPSS Statistics for Windows. IBM Inc., Armonk, New York Quantitative variables were defined using means and standard deviations, whilst categorical variables were reported using absolute frequencies and compared using the chi-square test. The trend test chi-square was used to ordinal binary data. To confirm the assumptions for parametric testing, Levene (homogeneity of variances) and Kolmogorov-Smirnov (distribution-type) tests were used. The independent sample t-test (for normally distributed data) and Mann-Whitney test (for not normally distributed data) were used to compare quantitative data between two groups.

The strength of the link between two continuous, non-normally distributed variables was evaluated using the Spearman rank correlation coefficient. To determine the likelihood that specific risk variables will result in specific health issues, binary logistic regression analysis was used. P 0.05 was chosen as the cutoff for statistical significance. If p 0.001, a highly significant difference was detected.

RESULTS

From 141 RA patients, females were more than 75%. They were between the ages of 22 and 74 years with the presence of the disease from six months up to forty-three years (Table 1). According to the type of anti-rheumatic drugs used; Patients were divided into two groups; **group I:** Forty-nine patients (34.75%) on conventional synthetic non-biological therapy (cs-DMARDs), while **group II:** 92 patients (65.25%) on biological therapy, of them, 40 (28.37%) on Golimumab [Simponi®], 36 (25.53%) on Etanercept [Enbrel®] and 16 (11.35 %) on Adalimumab [Humira®] (Table 2).

Table (1): Descriptive data of the studied RA patients

141 RA patients			
Age (Years)	**Range**	22 – 74	
	Mean ±SD	50.404 ± 11.945	
DD (Years)	**Range**	0.5 – 43	
	Mean ±SD	10.631 ± 6.671	
		N	**%**
Sex	**Male**	32	22.70
	Female	109	77.30
WBCS (/mm^3)	**Mean ±SD**	7.136±1.691	
Neutrophils (/mm^3)	**Mean ±SD**	4.287±0.921	
Lymphocyte (/mm^3)	**Mean ±SD**	2.283±0.390	
HCT (%)	**Mean ±SD**	36.149±2.364	
RBCs (million/mm^3)	**Mean ±SD**	4.786±0.523	
Hb (g/dL)	**Mean ±SD**	11.984±0.810	
MCV (fl)	**Mean ±SD**	78.865±7.346	
MCH (pg)	**Mean ±SD**	26.457±3.021	
RDW (%)	**Mean ±SD**	13.776±2.234	
PLT (/mm^3)	**Mean ±SD**	402.752±97.647	
MPV (fl)	**Mean ±SD**	9.177±1.009	
PDW (%)	**Mean ±SD**	10.445±1.655	
Hb/PLT ratio	**Mean ±SD**	0.037±0.008	
RDW/PLT ratio	**Mean ±SD**	0.040±0.010	
RBCs/PLT ratio	**Mean ±SD**	0.015±0.003	
Hb/RDW ratio	**Mean ±SD**	0.896±0.177	
NLR	**Mean ±SD**	2.086±0.421	
PLR	**Mean ±SD**	199.045±7.361	

Table (2): Drugs received by the studied patients

141 RA patients			
		N	**%**
CS		141	100.00
MTX		141	100.00
HCQ		138	97.87
Cellcept		2	1.42
Leflunamide		139	98.58
Non-Biologics		49	34.75
Biologics		92	65.25
Types of biologics	**Enbrel**	36	25.53
	Simponi	40	28.37
	Humira	16	11.35
Duration biologics (Months)	**Range**	3 -	48
	Mean ±SD	7.772 ±	8.030

CS: Corticosteroid, **MTX:** Methotrexate, **HCQ:** Hydroxychloroquine, **MMF:** Mycophenolate mofetil, **No**: number, **%:** percentage.

Comparison between both groups regarding the hematological indices showed that regarding the WBCs parameters; patients on biological therapy had lower total WBCs and neutrophils count with higher lymphocyte count yet the change fell short of the levels of statistical significance. As regard RBCs parameters; patients on biological therapy resulted in a statistically significant decrease in RDW, and a statistically significant increase in hematocrit. Hb concentration, RBCs count and MCV with lower MCH were increased but didn't reach the statistical significance. Comparing the platelets parameters; patients on biological therapy had statistically significant lower platelet count and PDW, while there were no considerable differences in MPV. There was a statistically significant higher Hb/PLT, RDW/PLT, RBCs/PLT, and Hb/RDW ratios, and statistically significant lower NLR and PLR in patients used biological therapy than those on cs-DMARDs (Table 3).

Table (3): Comparison between group I and II as regard Hematological parameters

	Group I Non-Bio;ogical Therapy No. (49)	Group II Biological Therapy No. (92)	T-Test	
	Mean ± SD	Mean ± SD	T	P-value
WBCS (/mm^3)	7.695 ± 1.72	6.838 ± 1.002	1.967	0.051
Neutrophils (/mm^3)	4.778 ± 1.108	4.026 ± 1.100	1.849	0.067
Lymphocyte (/mm^3)	2.262 ± 0.451	2.294 ± 0.321	-0.265	0.791
HCT (%)	35.532 ± 2.395	36.477 ± 2.292	-2.294	0.023*
RBCs (million/mm^3)	4.772 ± 0.540	4.794 ± 0.516	-0.230	0.818
Hb (g/dL)	11.859 ± 0.718	12.050 ± 0.852	-1.335	0.184
MCV (fl)	78.773 ± 8.341	78.914 ± 6.805	-0.108	0.914
MCH (pg)	26.876 ± 3.271	26.235 ± 2.873	1.201	0.232
RDW (%)	15.455 ± 1.410	12.882 ± 2.075	7.773	<0.001**
PLT (/mm^3)	518.755 ± 121.815	340.967 ± 81.312	6.565	<0.001**
MPV (fl)	9.251 ± 1.192	9.137 ± 0.902	0.633	0.528
PDW (%)	10.878 ± 1.873	10.215 ± 1.487	2.297	0.023*
Hb/PLT ratio	0.025 ± 0.004	0.044 ± 0.011	-5.987	<0.001**
RDW/PLT ratio	0.031 ± 0.003	0.044 ± 0.010	-5.379	<0.001**
RBCs/PLT ratio	0.010 ± 0.001	0.018 ± 0.0032	-6.403	<0.001**
Hb/RDW ratio	0.773 ± 0.089	0.962 ± 0.177	-6.990	<0.001**
NLR	2.558 ± 0.326	1.845 ± 0.352	2.734	0.007*
PLR	272.712 ± 64.331	161.277 ± 37.021	4.863	<0.001**

RA: Rheumatoid arthritis, **WBCs:** White blood cells, **HCT:** Hematocrit, **RBCs:** Red blood cells, **Hb:** Hemoglobin, **MCV:** Mean corpuscular volume, **MCH:** Mean corpuscular Hemoglobin, **RDW:** Red cell distribution width, **PLT:** Platelets, **MPV:** Mean platelet volume, **PDW:** Platelet distribution width, **Hb/PLT ratio:** Hemoglobin/Platelet ratio, **RDW/PLT ratio:** Red cell distribution width/ Platelet ratio, **RBCs/PLT ratio:** Red blood cells/Platelet ratio, **Hb/RDW ratio:** Hemoglobin/ Red cell distribution width ratio, **NLR:** Neutrophil/Lymphocyte ratio, **PLR:** Platelet/Lymphocyte ratio, **mm^3:** Per cubic millimeter, **%:** percentage, **g/dL:** Gram per deci Liter, **fl:** femtoliter, **pg:** picogram, **mm/h:** millimeter per hour, **mg/L:** milligram per Liter, **IU/ml:** International unit per milliliter, **U/L:** Unit per liter, **mg/dL:** milligram per Deci Liter , **t:** independent sample t test, **P**: probability value, ***:** $p<0.05$ is statistically significant, ****:** $p\leq0.001$ is statistically highly significant, **SD:** Standard Deviation.

Additionally, we correlated the duration of biological therapy intake with various hematological parameters (Table 4). We discovered statistically significant link between the duration of biological therapy and the values of Hb concentration, total platelet count, and their related ratios (/PLT, RDW/PLT, RBCs/PLT, and Hb/RBCs), as well as RDW and MPV.

Table (4): Correlation of duration of biologic therapy with different hematological parameters

	Duration biologics (Months)	
	R	P-value
WBCS (/mm^3)	-0.135	0.200
Neutrophils (/mm^3)	-0.071	0.501
Lymphocyte (/mm^3)	0.045	0.670
HCT (%)	0.115	0.276
RBCs (million/mm^3)	0.017	0.869
Hb (g/dL)	0.393	<0.001**
MCV (fl)	0.127	0.229
MCH (pg)	-0.027	0.798
RDW (%)	-0.319	0.002*
PLT (/mm^3)	-0.330	0.001**
MPV (fl)	-0.236	0.024*
PDW (%)	0.016	0.880
Hb/PLT ratio	0.439	<0.001**
RDW/PLT ratio	0.362	<0.001**
RBCs/PLT ratio	0.360	<0.001**
Hb/RDW ratio	0.429	<0.001**
NLR	0.047	0.659
PLR	-0.195	0.062

DISCUSSION

Suppressing local and systemic inflammatory responses is the primary goal of RA therapy. Recently with the expand use of the biological therapy, some researchers started to study the hematological impact of these therapies and its possibility to induce hematological side effects that may affect patient's condition [5]. In this research we aimed to assess the hematological impact of biological therapy in RA in comparison to cs-DMARDs.

Regarding the WBCs parameters, there were lower total WBCs and neutrophil count in biological therapy group, which was in line with many other studies [5, 13, 17-18]. The majority of research have revealed that a decline in WBC and neutrophil count occurs concurrently with the reduction of inflammation brought on by the use of biological therapy. We detected greater lymphocyte counts with biological therapy similarly to other studies [5, 13, 19-20].

The development of lympho-proliferative diseases and pathological abnormalities could be explained by the fact that anti-TNF drugs have a dual effect in hematopoietic stem and progenitor cell proliferation [5, 13, 19–20]. Moreover, there is a negative correlation between RA activity and lymphocyte counts, suppression of RA activity by effective treatment is accompanied by increase in the lymphocyte count [5]. Neutrophil levels, in contrast to lymphocytes, are elevated in chronic inflammatory illnesses (such as RA), and they will decrease with appropriate treatment as will the WBC count [19].

We found that most of our patients suffered from anemia particularly the microcytic hypochromic type. Different types of anemia are often present in RA patients due to many mechanisms as pathogenic iron homeostasis and/or impaired erythropoiesis [21]. Surprisingly, treatment with anti-TNF therapy showed higher RBCs and Hb parameters (RBCs count, Hb concentration, MCV and hematocrit value) and this was also reported by other researchers [22,23].

This increase can be explained by the negative correlation between the Hb and RBCs values with disease activity. Reduction of inflammation by the potent anti-inflammatory effect of the biological therapy, will result in improvement in inflammatory anemia, particularly the microcytic hypochromic type. Increased levels of hepcidin and serum ferritin are thought to be the cause of higher levels of iron storage and decreased levels of serum iron, according to **Song and his colleague** [24].

Hence, it is feasible that utilizing anti-TNF agents could contribute to lowering hepcidin and ferritin levels, leading to a reduction in anemia as a result of increased blood iron availability for erythrocyte and hemoglobin synthesis [22]. In contrast to prior study [5] who found decreased RBCs parameters in patients used biological therapy, this study reported that patients receiving Etanercept and Adalimumab had significantly lower RBCs and Hb levels than in healthy donors or other biological therapy and this was in line with our results.

It is widely recognized that platelets are crucial in RA pathophysiology [25]. In inflammation when combined with other parameters like ESR and CRP, a rise in platelet count is an indication of the acute phase response, these are critical indicators of the disease's activity and the efficacy of treatment [26]. In contrast to non-biological users, our data showed that biological therapy causes a statistically significant decrease in platelet count and PDW [5, 13, 23, 27].

This decrease is occurring with the decrease of the other inflammatory markers (ESR and CRP) as a result of decrease in the disease activity due to the potent anti-inflammatory effect of the biological therapy. The MPV values was similar in both groups and both have normal ranges of platelet volumes, which reflects that the platelet sizes were improved with treatment in both groups and also reflects the effectiveness of both therapy in reduction of disease activity. Our results agreed with the observation of Bath and Butterworth in 1996 [28] and **Gasparyan and his colleague** in 2010 [27] who recognized that there is correlation between platelet activation, count, volume (MPV), and diameter width (PDW) and these parameters were improved with effective treatment [11, 23, 27-28].

As a result, MPV and PDW have increased in value and are now a promising indicator of inflammation in several rheumatic disorders [29]. It appears that RA patients who are in active state of the disease have smaller platelets than those who are in remission. By preventing megakaryopoiesis, excessive pro-inflammatory cytokines might limit platelet size [28].

Understanding that interaction between RBCs and platelets may be useful in assessing RA inflammation. In the current research, individuals receiving biological therapy had significantly different values for several RBCs and platelet-related ratios (Hb/Plat, RDW/Plat, RBCs/Plat, and Hb/RDW ratios) than did patients receiving non-biological therapy. To our knowledge no studies focused on this point. In our study, the patients on biological therapy had higher RBCs related parameters (Hb, RBC count, MCV, hematocrit values) and lower platelet related parameters (Platelet count and PDW), and this what makes the significant difference in ratios. Additionally, this reflects that these ratios might reflect the level of disease activity and inflammation. These findings concurred with many previous studies [22, 23, 27].

The NLR and PLR ratios was significantly lower in patients used biological therapy than non-biological therapy and this agreed with many other studies [5, 23]. This reflects and proves the potent and effective anti-inflammatory action of the biological therapy and its value in inflammation suppression. Complete blood count parameters especially

neutrophils, lymphocytes and platelets, play important roles in evaluating many inflammatory diseases [30]. In many recent studies, several authors suggested the use of NLR and PLR ratios as suitable and simple biomarkers of systemic inflammation and disease activity associated with numerous diseases including RA. In addition, NLR and PLR have an established correlation with ESR, CRP, TNF-α, and DAS scores [31-34].

Finally, while comparing the duration of use of biological therapy with various hematological indicators, we discovered a statistically significant correlation. This correlation supports the positive effect on maintain therapy on biologics based on its potent role anti-inflammatory effect as well as their subsequent hematological effect. To our knowledge, there were no studies that focused on this aspect.

Yet, this study had significant limitations because it was a retrospective examination of the data on RA patients and selection bias cannot be totally eliminated. Also, only 141 RA patients from a single center were included in this study. To verify the correctness of the findings, a multi-center prospective study with a sizable sample is still necessary.

CONCLUSION

Biological therapy had obvious effects on hematological parameters, and these effects were related partially to the potent nature of these group of drugs and partially related to the nature of each therapeutic agent. Additionally, these hematological effects were in strong correlation with the duration of biological use.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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