Clinical Evaluation and Comparison between Effects of Rituximab and Prednisolone with Imuran to Neutrophils and Platelet Counts in Pemphigus Vulgaris Patients

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Abstract

Background: Pemphigus vulgaris (PV) is an autoimmune vesiculobullous mucocutaneous disease with life-threatening consequences. Rituximab (RTX) has recently emerged as an effective treatment for PV. **Objectives:** This study aims to determine changes in neutrophil and platelet counts for PV patients treated with RTX or corticosteroids combined with Imuran (azathioprine). **Materials and Methods:** The present cross-sectional study was conducted in the Department of Dermatology at Baghdad Teaching Hospital, Baghdad, Iraq. Thirty PV patients received two types of treatment: 15 patients were administered RTX and 15 patients took corticosteroids with Imuran (azathioprine). Neutrophil and platelet counts were detected at the hospital laboratory. **Results:** The age range of PV patients was 27–67 years, and the mean ±SD was 44.866 ± 10.979 years for the patient group treated with RTX and 44.133 ± 11.519 for the patient group treated with corticosteroids and Imuran. In patients treated with RTX, 26.6% were males and 73.33% were females, with a female-to-male ratio of 2.75:1. In patients treated with corticosteroids with Imuran, 40% were males and 60% were females, with a female-to-male ratio of 1.5:1. The results revealed that among patients treated with RTX, 30% of them had mucocutaneous lesions, 6.66% had oral lesions, and 13.33% had cutaneous lesions. Among the other groups treated with corticosteroids and Imuran, 23.33% had mucocutaneous lesions, 13.33% had oral lesions, and 13.33% had cutaneous lesions. Among the patients treated with RTX, 53.33% had normal range of neutrophil count, while 46.6% had neutrophil count above the NR, while in patients treated with corticosteroids and Imuran, 40% had a normal range and 60% had above the normal range. **Conclusion:** RTX was a more effective treatment compared to corticosteroids with Imuran because no patient remained in an active state during this study. PV was prevalent in females aged 40 years with mucocutaneous lesions.

Keywords: Neutrophils, pemphigus vulgaris, platelets, rituximab

Introduction

Pemphigus vulgaris (PV) is an autoimmune vesiculobullous mucocutaneous disease with life-threatening consequences. It is a rare disease, with incidence ranging from 0.07 to 1.6 per one million people/year and an uneven geographic distribution. Delayed diagnosis and inadequate treatment of PV can endanger the patient's life.[1]

The disease is characterized by the presence of autoantibodies directed against structural proteins in the human skin.[2] The presence of autoantibodies in the patient's circulation or in the intercellular spaces of the epidermis or epithelium leads to acantholysis, erosion, and blister formation on the skin and/or mucus membranes and has a high affinity to rupture[3,4] [Figures 1–3].

The diagnosis of pemphigus vulgaris depends on clinical manifestations, and a biopsy was used for histopathological investigation to distinguish the presence of Ig autoantibodies in the tissue section by a direct immunofluorescence assay

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/mjby
	DOI: 10.4103/MJBL.MJBL_15_23

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Submission: 05-Jan-2023 **Accepted:** 22-Jan-2023 **Published:** 17-Jul-2024

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How to cite this article: Al-Drobie B, Abdul-Qahar GH, Al. Aswad FD, Al-Hasnawi ZA. Clinical evaluation and comparison between effects of rituximab and prednisolone with imuran to neutrophils and platelet counts in pemphigus vulgaris patients. Med J Babylon 2024;21:251-8.

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Figure 1: Skin ulcer

Figure 2: Mouth ulcer

Figure 3: Skin ulcer

(DIF).[5] Indirect immunofluorescence (IIF) antibody tests are performed on a patient's serum for differentiating PV from pemphigoid and other chronic oral lesions and in follow-up improvement during management.[6]

An enzyme-linked immunosorbent assay (ELISA) is more sensitive than IIF and can differentiate antiDSG1 antibodies from antiDSG3 antibodies in serum samples. The ELISA can differentiate PV from pemphigus foliaceous and may be helpful in determining disease activity and prognosis. Latest work has shown that saliva is actually a useful alternative to serum for ELISA testing, with desmoglein 3 IgG detectable in saliva by ELISA, which has a similar sensitivity to serum (61% saliva vs. 74% serum).[6]

In general, there is no exact protocol for PV treatment. However, corticosteroids and adjunctive treatments are usually prescribed.[2] The most favorable new treatment for many autoimmune diseases is the monoclonal antibody rituximab (RTX). The information about the therapeutic nature of RTX (which is now used for PV) was first discovered in 2002 for treatment of lymphoma, which was the only approved protocol at that time, and it remains to be used in this way with significant success.[7]

Later, RTX was approved in the United States for rheumatoid arthritis (RA) at a different dosing program.[8] The first formed from two 1000-mg infusions with a 2-week interval in adults, regardless of body weight. This dosage offers the benefit of requiring fewer infusions.[9] The second was designed in sessions; in each session, RTX was given in a dose of 375 mg/m^2 four doses (one dose each week). The first infusion is given slowly for about 8 h, and subsequent infusions took 4 h.[10]

RTX is a chimeric IgG1 monoclonal antibody against CD20, a transmembrane glycoprotein, expressed exclusively on the surface of almost all B cells. It induces a temporary depletion of CD20 B cells in peripheral blood within a few hours.[11] Before treatment with RTX, analgesic/antipyretic (e.g., paracetamol), an antihistaminic drug (e.g., chlorphenamine), and glucocorticoids (e.g., methylprednisolone) must be given to reduce or avoid infusion reactions.[12]

Despite notable differences in autoimmune pathological mechanisms and presentation of clinical symptoms, neutrophils have been shown to play a role in the pathology of numerous autoimmune diseases. This is not unexpected considering their wide range of functions, their biotoxicity, and sheer abundance in circulation. Neutrophils are capable of causing much collateral destruction to the surrounding tissue when activated in the context of autoimmunity as they are rapidly sent to the site of inflammation and release their antimicrobial and immunomodulatory functions.[13]

Platelets have a communal ancestral cell, the thrombocyte, which plays both hemostatic and immune roles in vertebrates. Therefore, it is no surprise that platelets frequently pervade immunologic functions. Although not strictly appointed within the inflammatory pathway, platelets can be observed as an extension of the cellular immune system. Recent evidence shows that platelets are involved in various inflammatory processes that influence normal leukocyte biology and inflammatory signals.[14]

According to our knowledge, this is the first study aimed at determining the association between changes in neutrophil and platelet counts in PV patients when they were treated with RTX or treated with corticosteroids with Imuran (azathioprine). The main goal for the study is to assess the effects of two types of treatment.

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Materials and Methods

This cross-sectional study was conducted from April to October 2022 in the Department of Dermatology at Baghdad Teaching Hospital. In this study, 30 patients were diagnosed with PV based on clinical examination by a dermatologist, and the biopsy sample was evaluated by a histopathologist (the H&E staining slides were evaluated for the histopathological features of PV, which include the presence of suprabasal separation, acantholysis, and Tzanck cells in the formed cleft)[15] [Figure 4].

Based on their level of approval, the researchers were permitted to contact patients when they visited the dermatology department. Consultations were conducted after obtaining verbal informed consent from patients who were able to follow instructions and willing to participate in the trial, and all questions in this study were asked in the patient's native language, and answers were acquired after clarifying the aim of the study for each patient. This study included patients treated with RTX and corticosteroids with Imuran. Any patients treated with another treatment or with a history of hematology disease were excluded.

Fifteen patients with PV were treated with RTX (MabThera, Roche) at a dose of 375 mg/m^2 in two doses every 2 weeks. Before administering RTX, patients were given acetaminophen and antihistamines to decrease the risk of infusion reactions. A major challenge was the high rate of infections, some of which were fatal. Therefore, patients should be carefully monitored during and after RTX therapy to avoid the development of complications. The other group of 15 patients were treated with corticosteroids and Imuran (azathioprine). The age and sex of the two groups were matched.

For each patient, the following data were recorded: age, gender, site of lesions, disease activity, type of PV (mucous, mucocutaneous, or cutaneous), and hematology test results for neutrophil and platelet counts. The normal values are as follows: neutrophil (NR) count (NR =1.8–7.5) and platelet count (NR = 150–400).[16]

For the patients in whom relapse occurred, they were re-treated at an additional cycle of two doses of RTX with a dose of 375 mg/m^2 at a 1-week interval, with complete remission after 6 months. The response to treatment was determined according to the definitions of an International Consensus Conference[17]:

- Complete remission (CR): no new lesions.
- Partial remission (PR): presence of new lesions that heal within 1 week.

The above two groups can be achieved either without or with minimal therapy (≤10 mg/day of prednisone equivalent and/or minimal adjuvant therapy for at least 2 months).

- Relapse: appearance of more than three new lesions by month that do not heal spontaneously within 1 week.

Statistical analysis

Statistical analysis was carried out using SPSS version 23.0 (SPSS, IBM Company, Chicago, IL, USA). Descriptive statistics including mean ± standard deviation (SD) had been employed for continuous variables, median, percent, frequency, and standard errors (SE) for categorical variables. For gender and age, the frequency and percentage of all patients were included in the study. The chi-square test was used to compare percentages to determine the association between dependent variables (sex and age) and independent variables (site of lesions and activity of PV). A significant level was set at P value ≤ 0.05. The normality of the distribution of all variables was evaluated by Student's (analysis of variation ANOVA) test, and analyses have been used to compare significant differences between means.[18]

Ethical approval

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. It was carried out with patients' verbal consent. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number Ref.434 in December 2021.

Results

Clinical findings

Age and sex distribution

Thirty PV patients participated in the present study. Their ages ranged from 27 to 67 years; 10 patients (33.33%) were males, and 20 patients (66.66%) were females, with the mean ±SD of 44.50 ± 11.063 years. The highest frequency of age was in the age group 40–49 years, of which five patients were males (16.6%) and eight were females (26.6%), with standard error (SE) = 2.01987 and a female-to-male ratio of 2:1.

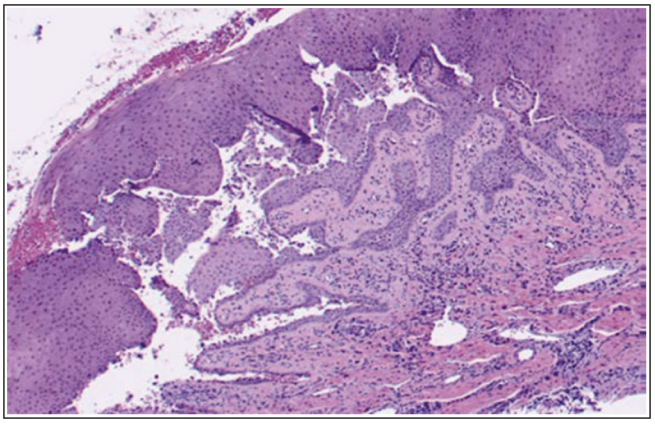

Figure 4: The H&E slides for PV biopsy

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In the present study, 15 individuals participated as PV patients treated by RTX. Their ages ranged from 27 to 67 years, 26.6% patients were male and 73.33% patients were female, with a mean ±SD of 44.866 ± 10.979. The highest frequency of age was distributed between the age range of 40 and 49 years, with one male patient (6.66%) and seven female patients (46.66%), a standard error (SE) = 2.83493, and a female-to-male ratio of 2.75:1, with *P* value 0.09 and chi-square value 0.3.

Fifteen individuals participated as PV patients treated by corticosteroids with Imuran (azathioprine). Their ages ranged from 27 to 65 years, 40% were males and 60% were females, and the mean ±SD was 44.133 ± 11.519. The highest frequency of age was distributed from 40 to 49 years, with four male patients (26.66%) and one female patient (6.66%). With standard error (SE) = 2.97428, and a female-to-male ratio of 1.5:1, with *P* value 0.4 and a chi-square 0.4. [Table 1].

Site of lesions

The results showed that among 30 PV patients who participated in the present study, with three sites of lesions, 16 patients (53%) had mucocutaneous lesions, 6 patients (20%) had oral lesions, and 8 patients (26.66%) had cutaneous lesions. *P* value = 0.3 with chi-square =0.6.

In the results for the 15 PV patients treated with RTX, nine patients (30%) had mucocutaneous lesions, two patients (6.66%) had oral lesions, and four patients (13.33%) had cutaneous lesions. *P* value = 0.3 with chi-square =0.6

In the results for the 15 PV patients treated with corticosteroids with Imuran, seven patients (23.33%) had mucocutaneous lesions and four patients (13.33%) had oral and cutaneous lesions. *P* value = 0.3 with chi-square =0.6 [Table 2].

Disease activity

The results showed that among 30 PV patients, there were four stages of disease activity: 13 patients (43.33%) in an active state, 9 patients (30%) had partial remission, 7 patients (23.33%) had disease relapse, and only 1 patient (3.33%) had complete remission.

Among 15 PV patients treated with RTX, the results showed that 1 patient (3.33%) had complete remission, 7 patients (23.33%) had partial remission and relapse, and no case with active state. χ^2 = 0.001** indicates a highly significant result.

In the results for 15 patients treated with corticosteroids and Imuran, 13 patients (43.33%) had active state, 2 patients (6.66%) had partial remission state, and neither complete remission nor relapse state was detected. χ^2 = 0.001** indicates a highly significant result [Table 3].

Laboratory findings

Regarding the neutrophil count, the results showed that among thirty PV patients, 14 (46.66%) had neutrophil count within the normal range of 1.8–7.5, while 16 patients (53.33%) had a neutrophil count of more than 7.5, with mean ± SD (7.9432 ± 3.50254), with standard error (SE) = (.63947).

In the results among the 15 PV patients treated with RTX, 8 patients (53.33%) had a normal range of 1.8–7.5, while 7 patients (46.6%) had a neutrophil count greater than 7.5, with mean ± SD (7.8117 ± 3.88576), with standard error (SE) = (1.00330).

The results among the 15 patients treated with corticosteroids and Imuran, 6 patients (40%) had normal range of 1.8–7.5, while 9 patients (60%) had neutrophil count greater than 7.5, with mean ± SD (8.0747 ± 3.20558), with standard error (SE) = (.82768). [Table 4].

Platelets

Regarding platelet count, the results showed that 29 of the patients (96%) were within the normal range of 150–400, while 1 patient (3.3%) had platelet count greater than 400, with mean ± SD (294.0633 ± 58.32125) and a standard error (SE) = (10.64796).

In the results for the 15 PV patients treated with RTX, 14 patients (93.33%) had normal range of 150–400, while 1 patient (6.6%) had platelets more than 400. The mean ± SD (326.1267 ± 57.55616) with a standard error (SE) = (14.86094). *P* value, *P* = 0.001** indicates a highly significant result.

In the results for the 15 patients treated with corticosteroids and Imuran, 15 of patients (100%) had normal range from 150.000 to 400.000, while no case had been detected with more than 400 count. with mean ± SD (262.0000 ± 39.11521), with a standard error (SE) = (10.09950) [Table 5]; *P* = 0.001** with high significant result [Table 5].

Discussion

This is the first study in Iraq aimed at determining the association between changes in neutrophil and platelet counts in PV patients treated with RTX or with corticosteroids with Imuran (azathioprine). This study has some limitations because PV is a rare autoimmune disease, and the sample size of the study population is small. Prolonged treatment with immune suppressing therapies can increase the risk of severe adverse effects.[19]

The average age of PV patients in this study was 44 years. This result was compatible with those of several previous studies worldwide.[20-22]

Also, another study in Brazil[23] indicated that the average age was between 41 and 44 years, which is less than that

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Table 1: The association between age and sex in the two groups of PV patients treated with rituximab and corticosteroids with Imuran

Age groups (years)	Group of patients treated by rituximab (no. 15)		Group of patients treated with corticosteroids with imuran (no. 15)		Total PV (no. 30)	
	Male	Female	Male	Female	M	F
20–29	0	2 (13.33%)	0	2 (13.33%)	0	4 (13.3%)
30–39	1 (6.66%)	1 (6.66%)	2 (13.33%)	1 (6.66%)	3 (10%)	2 (6.66%)
40–49	1 (6.66%)	7 (46.66%)	4 (26.66%)	1 (6.66%)	5(16.6%)	8 (26.6%)
50–59	0	1 (6.66%)	0	3 (20%)	0	4 (13.3%)
60–69	2 (13.33%)	0	0	2 (13.33%)	2(6.66%)	2 (6.66%)
Sum	4 (26.6%)	11(73.33%)	6(40%)	9(60%)	10(33.33%)	20(66.66%)
F:M	2.75:1		1.5:1		2:1	
Mean± SD	44.866 ± 10.979		44.133 ± 11.519		44.5000 ± 11.06330	
Std. error of mean	2.83493		2.97428		2.01987	
Maximum	67		65		67	
Minimum	27		27		27	
P value	0.09 NS		0.4 NS		-	
Chi-square	0.3 NS		0.4 NS		-	

NS: non-significant.

Test: one-way ANOVA. Chi square = non-significant; *P* value = non-significant ($P \leq 0.05$)

Table 2: The association between the site of lesions and the two groups of PV patients treated with rituximab and corticosteroids with Imuran

Groups	Site of lesions			Total	*P* value & Chi-square
	Mucocutanuas	Oral	Cutaneous		
Rituximab group	9 (30%)	2 (6.66%)	4 (13.33%)	15 (50%)	$P = 0.3$
Corticosteroid with Imuran group	7 (23.33%)	4 (13.33%)	4 (13.33%)	15 (50%)	$\chi^2 = 0.6$
Total	16 (53%)	6 (20%)	8 (26.66%)	30 (100%)	NS

NS: non-significant.

Chi square = non-significant; *P* value = non-significant ($P \leq 0.05$)

Table 3: Association between the activity of the disease and two groups of patients treated with rituximab and corticosteroids with Imuran

Groups	Activity of disease				Total	Chi-square
	Active	Complete remission	Partial remission	Relapse		
Rituximab	0	1 (3.33%)	7 (23.33%)	7 (23.33%)	15 (50%)	0.001**
Corticosteroids with Imuran	13 (43.33%)	0	2 (6.66%)	0	15 (50%)	
Total	13 (43.33%)	1 (3.33%)	9 (30%)	7 (23.33%)	30 (100%)	

**High significant

reported by Serwin *et al.*[24] suggested that the average age was between 50 and 55 years. Other studies conducted in Croatia and[25] in Japan[26] show this result. The variation in results could be due to differences in study sample size and ethnic variations.

This study shows similarity to many previous studies that have the same result that females are more susceptible to PV than males in Iraq,[20] Slovakia,[27] and Morocco.[28] The high prevalence of autoimmune diseases in females can be explained by hormonal factors (estrogens and progesterone), immunological factors, and genetic factors (specific genes encoded on the X chromosome) by affecting the susceptibility to autoimmune disease. These have a severe activity during pregnancy and relapses in the postpartum period. In contrast, studies have indicated that males have a higher incidence of PV than females.[29] Findings revealed no significant differences between male and female patients in the two groups of PV patients studied.

The mucocutaneous lesions is the main site affected in both groups of patients when treated with RTX or corticosteroids with Imuran. Oral lesions are the less affected site for two groups, especially in the group treated with RTX. There is no significant difference between the

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Table 4: The association between neutrophil count and the two groups of patients treated with rituximab and corticosteroids with Imuran

Neutrophil count NR = 1.8–7.5	PV $N = 30$	Group of patients treated by rituximab ($N = 15$)	Group of patients treated with corticosteroids with imuran ($N = 15$)
1.8–7.5 (normal range)	14 (46.66%)	8 (53.33%)	6 (40%)
>7.5 (neutrophilia)	16 (53.33%)	7 (46.6%)	9 (60%)
mean ± SD	7.9432 ± 3.50254	7.8117 ± 3.88576	8.0747 ± 3.20558
Std. error of mean	0.63947	1.00330	0.82768
P value	$P = 0.8$ NS		
Chi square	$\chi^2 = 0.4$ NS		

NS: non-significant.

Chi square = non-significant; *P* value = non-significant ($P \leq 0.05$)

Table 5: The association between platelet count and the two groups of PV patients treated with rituximab and corticosteroids with Imuran

Platelets count NR = 150–400	PV $N = 30$	Group of patients treated with rituximab ($N = 15$)	Group of patients treated by corticosteroids with imuran ($N = 15$)
150–400 (normal range)	29 (96%)	14 (93.33%)	15 (100%)
>400,000 (thrombocytosis)	1 (3.3%)	1 (6.6%)	0
mean ± SD	294.0633 ± 58.32125	326.1267 ± 57.55616	262.0000 ± 39.11521
Std. error of mean	10.64796	14.86094	10.09950
P value	$P = 0.001^{**}$		

**Highly significant

two groups. This result may have similarity with a previous Iraqi study that said that during the period of follow-up of PV patients treated with RTX, no new lesions appeared. Oral lesions healed first, followed by trunk lesions, and scalp lesions were the last to be healed.[12] The main antigens in PV are desmogleins (Dsg) 1 and 3, which are expressed in the skin and mucosal tissue. The distribution of the two proteins varies in different epithelia, such that in skin, there is a high level of expression of Dsg 1 throughout the epidermis. In the oral epithelium, Dsg 3 is expressed through all layers. In PV, where anti-Dsg 3 antibodies are predominant, there is generally marked mucosal blistering.[30] Both RTX and the comparator high-dose corticosteroid with Imuran cause a reduction in auto-antibodies anti-Dsg 1,3 to a similar extent in the first 12 months of treatment. After 12 months, RTX better maintained the reduction of these auto-antibodies than high-dose corticosteroids.[30] After treatment, the baseline titers of anti-Dsg1,3 decreased within 3 months to similarly low levels within 3 months in both groups (RTX and corticosteroid). In the corticosteroid-only group, the titers of anti-Dsg3 started to increase again after 12 months, although they did not return to baseline level in 24 months. Anti-Dsg1 titers remained low over 24 months in both groups.[31] This difference may lead to our result because limited pharmacokinetic data have been obtained until now.

There is a highly significant difference between the two groups of PV patients according to the activity of the disease because there is no patient in an active state, and one patient has complete remission in the RTX group compared to the prednisolone with Imuran group in which main patients are in an active state. This result is pertinent to that of a previous Iraqi study which found that the main patients treated with RTX had complete remission.[12] Also, in France, Reguiai *et al*.[32] found that the main patients treated by RTX have complete remission. Recently, in India, Hassan *et al*. found that clinical improvement in symptoms was noted in just over a month, and 87.5% of the patients achieved CR off-therapy within 6.36 months following the second dose.[33] The mechanism of the efficacy of treatment with RTX discussed by the European Medicine Agency in 2019 showed the effective use of RTX in severe and refractory pemphigus due to its B cell-depleting effect. In PV patients treated with RTX, it has been observed that profound peripheral B cell depletion occurs by 3 weeks, and B cell reconstitution begins approximately 6 months after RTX treatment. Also, a dramatic decrease in anti-Dsg1,3 IgG antibodies was detected after treatment with RTX in eight out of twelve patients who achieved complete remission (CR) and was associated with the blockage of B cell maturation, repopulation with naïve and transitional B cells, delayed reappearance of memory B cells, and withdrawal of desmoglein-specific IgG + B cells.[31]

Autoimmune disease is supposed to result from complex interactions between T-lymphocytes, neutrophils,

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macrophages, mast cells, keratinocytes, and dendritic cells. Neutrophils initiate the first step of systemic inflammation and exhibit nonspecific inflammation.[34] In 2022, Kowalska-Kępczyńska *et al*.[35] reported that changes in the number of individual WBCs during pemphigus activation are due specifically to the stimulation of immunocompetent cells during inflammation.

The nonsignificant correlation between neutrophil and two treatment groups of treatments in this study is explained by the fact that RTX and corticosteroids are immunosuppressive treatments that greatly affect the number of neutrophils. The increase in the number of neutrophils in this study could be explained by the fact that in healthy individuals, about half the population of WBCs in the blood circulation are neutrophils, also known as neutrophil granulocytes. These phagocytes are part of primary immunity. Following an inflammatory stimulus, changes in neutrophil morphology and motility occur due to the stimulation of different immune response strategies. Depending on the trigger of the inflammatory process, neutrophils may undergo phagocytosis, secretion of a number of proinflammatory cytokines, or release of neutrophil extracellular traps.[35]

The highly significant relationship of platelets in this study shows a role in many processes such as immunity and inflammation. Platelet counts can decrease in the body's immune system mistakenly attacks and destroys platelets. Additionally, infections by bacteria and viruses can temporarily lower platelet counts, and platelets can increase when the disease triggers. Also, this can lead to infection.[36]

Conclusion

When treating PV patients with RTX or corticosteroids such as Imuran (azathioprine), neutrophils were affected more than platelets. This effect is even more pronounced when using RTX. RTX is a more effective treatment compared to corticosteroids with Imuran, as no patient was still in an active state during this study. PV was prevalent in 40-year-old female with mucocutaneous lesions even with effective therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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