Orginal Article

Eosinophil and Monocyte Counts as Hematological Markers for Response to Tetracyclines for Treating Bullous Pemphigoid

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Abstract

Aim: Tetracyclines are used in bullous pemphigoid (BP) treatment because of their anti-inflammatory properties. We investigated the effects of tetracyclines on blood cell counts, which serve as inflammatory markers, in patients with BP.

Materials and Methods: The study included 50 patients with BP who were treated with tetracycline group antibiotics and followed up for an average duration of 3.1±1.2 months in a university hospital between January 2013 and December 2022. Demographic data, comorbidities, medications, physical examination findings, treatment responses, and hematological parameters before and after treatment were retrospectively recorded.

Results: The median blood eosinophil count (450 cells µL-1; range: 0-430) and the mean blood monocyte count (660 cells µL-1; range: 300-1100) of the 50 patients with BP were significantly higher than those of the healthy age- and gender-matched Turkish population ($P < 0.001$; $P = 0.01$; respectively). At the end of the follow-up period, 30 patients were in remission, whereas relapses occurred in 20 patients. The eosinophil and monocyte cell count, eosinophil-to-lymphocyte ratio (ELR), and C-reactive protein (CRP) levels in patients who were in remission were significantly lower compared to those pre-treatment ($P = 0.001$, $P = 0.02$, $P < 0.001$, $P = 0.001$, respectively). There was no significant difference between the doxycycline and tetracycline treatment groups regarding the odds of remission after treatment [odds ratio: 2 (95% confidence interval: 0.5-7.3)].

Conclusion: Higher levels of circulating monocytes indicate their role in the pathogenesis of BP. Peripheral eosinophil count, ELR, and monocyte count, along with CRP, could serve as markers for monitoring the response to tetracyclines and the risk of relapse in patients with BP.

Keywords: Eosinophil and monocyte count, anti-inflammatory effect, bullous pemphigoid, hematological parameters, tetracycline group antibiotics

Introduction

Bullous pemphigoid (BP), the most common autoimmune blistering skin disease, is characterized by autoantibodies against the hemidesmosomal proteins BP180 and BP230. Recent studies have indicated a 2-to 4-fold increase in the incidence of BP.[1,2] A multicenter study in Turkey has estimated that the incidence of pemphigoid diseases increases with age, with an overall incidence rate of 3.55 cases per 1,000,000.[3] The clinical presentation is characterized by itchy urticarial plaques and tense bullae on the trunk and extremities although some patients may only experience itching. The disease predominantly affects the elderly population.[4]

According to the European guidelines, the recommended first-line treatment for mild, moderate, and severe pemphigoid disease includes superpotent topical corticosteroids applied to the entire body at 20-40 g/day. In severe cases, oral prednisolone is the standard treatment. Alternatives to prednisolone treatment include agents such as azathioprine, mycophenolate mofetil, dapsone, doxycycline, methotrexate, and mycophenolate mofetil, either alone or in combination with oral corticosteroids.[5]

Tetracyclines are broad-spectrum antibiotics that inhibit protein synthesis at the ribosomal stage.[6] Beyond their antimicrobial

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effects, they have biological effects on inflammation, proteolysis, angiogenesis, apoptosis, metal chelation, ionophoresis, inhibition of immunoglobulin E (IgE) synthesis, and bone metabolism. Therefore, their use in rosacea, bullous dermatoses, neutrophilic disorders, pyoderma gangrenosum, sarcoidosis, aortic aneurysm, metastatic cancer, periodontitis, and rheumatoid arthritis has been explored.[7] Doxycycline has also been reported to inhibit leukocyte chemotaxis, reduce the release of inflammatory cytokines, and decrease the production of pathogenic nitric oxide.[8] Tetracyclines are used in BP treatment for their anti-inflammatory properties.[9]

A multicenter, parallel group randomized controlled trial demonstrated that doxycycline was not inferior to oral prednisolone concerning the effectiveness and safety in the long term.[9] However, the effects of tetracyclines on blood cells in patients with BP remain unknown. Inexpensive, non-invasive, and easily applicable hematological parameters have been used as new inflammatory markers in various inflammatory, cardiovascular, and malignant diseases.[10] This study aimed to evaluate the effect of tetracyclines on blood cell counts serving as inflammatory markers in patients with BP.

Materials and Methods

The study included 50 patients with BP treated with tetracycline group antibiotics and followed up in a specialized outpatient clinic for autoimmune blistering diseases in a university hospital between January 2013 and December 2022. The diagnosis of pemphigoid was established with the clinical presence of tense vesiculobullous, urticarial lesions and/or nodular lesions with excoriated surfaces, observation of a subepidermal blister with eosinophils in both the blister cavity and dermis on histological examination, and the presence of linear C3 ± IgG accumulation in the basal membrane zone on direct immunofluorescence examination. Patients with active infection or malignancy or those receiving systemic steroids and other immunosuppressive treatments were excluded from the study. The baseline disease severity of patients was determined on the basis of the involvement of body surface area.[11] The involvement of less than 10% of the body surface area was considered mild, 10-30% moderate, and more than 30% severe. The outcome measures used in monitoring BP were based on the recommendations of the international panel published by Murrell et al.[12] In a patient with controlled disease, the appearance of three or more new lesions a month (bullae, eczematous lesions, urticarial plaques) that do not heal spontaneously in one week, extension of existing lesions, or daily complaints of pruritus were considered as relapse. Twenty-six patients were started on 2x200 mg/day doxycycline, while 24 patients were received 4x500 mg tetracycline treatment. In addition, all patients were administered superpotent topical corticosteroid treatment from the first day of therapy.

Demographic data, comorbidities, medications, physical examination findings, treatment responses, hematological parameters before and after the treatment; neutrophil, lymphocyte, monocyte, platelet, eosinophil counts, and red cell distribution width, mean platelet volume (MPV), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and remission status at the end of the treatment were retrospectively recorded from the patient files. The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and eosinophil-to-lymphocyte ratio (ELR) were calculated from these parameters. Complete blood count was measured using the Beckman Coulter DxH 800 with impedance method features. CRP was determined using the Beckman Coulter AU 5800, which is capable of turbidimetric testing. The ESR was determined using photometric capillary flow kinetic analysis with the ALIFAX test 1 device.

Clinical data were evaluated after the approval of the Dokuz Eylül University Non-interventional Research Ethics Committee (approval number: 2022/42-01, date: 28.12.2022). Because of the retrospective nature of the study, informed consent of the patients was not required.

Statistical analysis

Data obtained at the end of the research were analyzed using the "Statistical Package for Social Sciences for Windows 24.0" program. Descriptive statistics were used to present the demographic and clinical characteristics of the study subjects. The normality of the continuous variables was evaluated using the Shapiro-Wilk test. The Wilcoxon test was used to compare the measurements of dependent groups, and the Mann-Whitney U test was used for independent groups. Independent samples t-test and Mann-Whitney U test were used to determine whether the blood monocyte and eosinophil counts of patients with BP differed from those of the healthy, age- and gender-matched Turkish population. All statistical tests were two-tailed, and a p value of less than 0.05 was considered statistically significant.

Results

The study included 33 women (66%) and 17 men (34%) with BP. The mean age was 70.9±13.2 years (range: 31-92 years). Patients were followed up for an average duration of 3.1±1.2 months (follow-up range: 2-8 months) after the initiation of tetracycline-class antibiotics. Fifty percent of the patients had moderate disease severity, whereas the other 50% had severe disease. Oral mucosal involvement was observed in

42% of the patients. The most frequent systemic disorders were hypertension (n = 36, 72%), diabetes mellitus (n = 28, 56%), coronary artery disease (n = 14; 28%), and kidney failure (n = 7; 14%). Alzheimer's disease was observed in 14% of the patients, and Parkinson's disease was observed in 4% of the patients. Diuretics were the most common drugs associated with pemphigoid and were used by 44% (n = 22) of the patients. A comparison of the rates of patients taking pemphigoid-associated drugs between the groups with remission and relapse is given in Table 1. During the treatment period, gastrointestinal irritation was the most common side effect (n = 12, 24%) observed in the patients, followed by an increase in transaminations (n = 10, 20%) and oral candidiasis (n = 5, 10%).

At the end of the follow-up period, 30 patients (60%) receiving tetracycline-class antibiotics were in remission, whereas relapses occurred in 20 patients (40%). The pre- and post-treatment hematological parameters of the patients are presented in Table 2. When hematological parameters were evaluated in the entire patient group, it was determined that there was a statistically significant decrease in eosinophil count, ELR, and CRP values at the end of the treatment period compared to pre-treatment ($P = 0.001$; $P < 0.001$; $P = 0.002$, respectively). After treatment, a significant decrease was observed in the eosinophil count, ELR, and CRP values in both the doxycycline and tetracycline groups.

The median blood eosinophil count of the 50 patients with BP (450 cells μL^{-1}; range: 0-430) was significantly higher ($P < 0.001$) than that of the healthy age- and gender-matched Turkish population (100 cells $\mu L^{-1;}$ range: 0-140). Compared with the same control group (560±180 cells μL^{-1}; range: 200-1000), the mean blood monocyte count of the patients with BP (660±180 cells μL^{-1}; range: 300-1100) was significantly higher ($P = 0.01$).

No significant difference was observed between the remission and relapse groups regarding basal eosinophil and monocyte

Table 1. Comparison of the rate of patients taking pemphigoid-associated drugs between the remission and relapse groups

Drugs associated with pemphigoid	Group with remission, (n = 30)	Group with relapse, (n = 20)	*P*
Likely or probable association, n (%)			
Gliptins	6 (20)	3 (15)	
Aspirin	7 (23.3)	0	
Furosemide + hydrochlorothiazide	16 (53.3)	6 (30)	
Losartan + lisinopril	14 (46.7)	7 (35)	
Total number of patients taking pemphigoid-associated drugs (%)	20 (66.7)	7 (35)	0.028*

*Pearson chi-square

Table 2. Comparison of hematological parameters of the patients between the pre and post-treatment

Haematological parameters	Pre-treatment Mean (range)	Post-treatment Mean (range)	*P**
Hemoglobin	12 (7.5-15.1)	12.7 (7.9-15.4)	0.01
MCV	86 (63.2-106.1)	87 (67-100)	0.7
Neutrophil count ($10^3/\mu L$)	5.2 (2.2-25.9)	4.8 (0.8-22)	0.80
Lymphocyte count ($10^3/\mu L$)	1.6 (0.7-9)	1.6 (0.3-3.4)	0.64
Eosinophil count ($10^3/\mu L$)	0.4 (0-4.3)	0.2 (0-2.6)	**0.001**
Monocyte count ($10^3/\mu L$)	0.7 (0.3-1.10)	0.6 (0.3-1.1)	0.083
Platelet count ($10^3/\mu L$)	267 (137-637)	255 (140-437)	0.58
RDW (%)	15 (12.7-22.6)	15.2 (13-23)	0.13
NLR	3 (0.6-11.3)	2.9 (0.5-44.6)	0.67
MLR	0.4 (0.06-1)	0.3 (0.1-2.6)	0.31
PLR	181 (30-420)	178 (79-933)	0.81
ELR	0.3 (0-1.4)	0.1 (0-2.6)	**0.000**
MPV	8.4 (6.6-11.6)	8.4 (6.8-11.8)	0.44
CRP (mg/dL)	12.6 (0.3-92.5)	5.7 (0.2-188)	**0.002**
ESH (mm/h)	23.5 (2-77)	20 (2-76)	0.176

*Wilcoxon signed-rank test, MCV: Mean corpuscular volume, RDW: Erythrocyte distribution width, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, ELR: Eosinophil-to-lymphocyte ratio, MPV: Mean platelet volume, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

counts (P = 0.773, P = 0.6; respectively). No significant difference was found in eosinophil counts between patients with moderate and severe BP (P = 0.81), and no correlation was observed (r=-0.03; P = 0.8).

A comparison of the hematological parameters according to groups with remission and relapse is given in Table 3. At the end of the treatment period, the eosinophil and monocyte cell counts, ELR, and CRP levels in patients who were in remission were significantly lower compared to pre-treatment (P = 0.001, P = 0.02, P < 0.001, P = 0.001, respectively). In the group with relapse, no significant statistical difference was found in these values compared to pre-treatment (respectively; P = 0.18, P = 0.94, P = 0.94, P = 0.35). There was no significant difference between the doxycycline and tetracycline treatment groups in terms of the odds of remission after treatment [odds ratio: 2 (95% confidence interval: 0.5-7.3)] (Table 4).

Discussion

In our study, the median basal peripheral eosinophil count in BP patients was significantly higher than that in healthy age- and gender-matched control groups. Approximately 50-60% of BP patients have peripheral eosinophilia in previous studies.[13,14] The presence of tissue and blood eosinophilia is one of the prominent findings in BP and is associated with inflammatory skin findings such as eczema and urticaria-like skin lesions. Moreover, eosinophils have been suggested to be the main source of the cytokine interleukin-31 (IL-31), which plays a key role in itch-related inflammation in BP.[15]

Table 3. Comparison of pre- and post-treatment hematological parameters in patients in remission and relapse

	Group with remission, n = 30 Mean (range)		*P*	Group with relapse, n = 20 Mean (range)		*P**
Haematolological parameters	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
Hemoglobin	12 (7.5-15)	12 (8.3-15)	0.15	12 (10-15)	13 (7.9-15)	0.002
MCV	87 (63-98)	88 (68-100)	0.76	85 (78-106)	85 (75-99)	0.185
Neutrophil count (10^3/µL)	5.3 (2.2-16)	4.8 (2.7-9)	0.41	5.2 (3.2-11)	4.8 (0.8-22)	0.49
Lymphocyte count (10^3/µL)	1.6 (1-9)	1.7 (0.9-3.4)	0.95	1.7 (0.7-3)	1.6 (0.3-3)	0.35
Eosinophil count (10^3/µL)	0.4 (0-2.6)	0.2 (0-1.2)	**0.001**	0.4 (0-4.3)	0.2 (0-2.6)	**0.186**
Monocyte count (10^3/µL)	0.7 (0.3-1)	0.5 (0.3-1)	**0.02**	0.6 (0.3-1)	0.6 (0.4-1)	**0.948**
Platelet count (10^3/µL)	265 (137-637)	252 (140-437)	0.45	279 (176-423)	264 (144-421)	1.0
RDW (%)	15 (13-22)	15 (13-23)	0.34	14 (13-18)	15 (13-18)	0.225
NLR	2.8 (0.64-11)	2.9 (1.1-7.4)	0.5	3.3 (1.3-5.8)	2.8 (0.5-4.4)	0.97
MLR	0.4 (0.06-0.7)	0.3 (0.1-0.9)	0.094	0.3 (0.2-1)	0.3 (0.2-2.6)	0.36
PLR	185 (30-352)	169 (85-303)	0.32	181 (89-420)	181 (79-933)	0.47
ELR	0.2 (0-1)	0.1 (0-1)	**<0.001**	0.3 (0-1.4)	0.2 (0-2.6)	**0.94**
MPV	8.6 (6.6-11.6)	8.5 (6.8-11.8)	0.93	8.1 (7.3-10)	8.2 (7.2-9.8)	0.189
CRP (mg/dL)	13.3 (0.3-81)	4.7 (0.2-135)	**0.001**	9 (0.6-92)	6.5 (2.5-188)	**0.35**
ESH (mm/h)	20 (2-77)	18 (2-63)	0.095	27 (7-75)	22 (3-76)	0.82

*Wilcoxon signed-rank test, MCV: Mean corpuscular volume, RDW: Erythrocyte distribution width, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, ELR: Eosinophil-to-lymphocyte ratio, MPV: Mean platelet volume, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

Table 4. Characteristics of patients in the treatment groups

	Doxycycline (n = 26)	Tetracycline (n = 24)	*P*
Age	67.5±12.3 (31-86)	74.6±13.4 (37-92) (ND)	0.032**
Sex			
Female	15 F	18 F	0.19
Male	11 M	6 M	
Pemphigoid disease severity	Moderate: 11 Severe: 15	Moderate: 13 Severe: 11	0.57
Oral mucosal involvement	Yes: 9 No: 17	Yes:12 No: 12	0.27
Remission rate after treatment period; n (%)	18 (69.2)	12 (50)	0.16*
OR (95% CI)	2 (0.5-7.3)	Ref.	

*P = 0.16 doxycycline versus tetracycline/pearson chi-square, **: Mann-Whitney U test, OR: Odds ratio, CI: Confidence interval, F: Female, M: Male

Gore Karaali et al.[16] have indicated that the eosinophil counts in the blood of patients with BP correlate with disease severity scores. The lack of correlation between eosinophil counts and disease severity in our study may be attributed to our patients consisting only of moderate and severe cases and the inability to retrospectively evaluate the BP area severity index.

In our study, the mean of baseline monocyte values in BP patients was significantly higher compared to the average of healthy control group. This suggests that circulating monocytes play a role in the pathogenesis of BP. BP is characterized by autoantibodies against BP180 and/or BP230, the component proteins of hemidesmosomes that connect basal epithelial cells to the underlying basement membrane. After the binding of autoantibodies to their target antigens, the complement cascade is activated. Subsequently, neutrophils and monocytes/macrophages accumulate at the dermoepidermal junction. These activated inflammatory cells release proteases such as neutrophil elastase and matrix metalloproteinase-9 (MMP-9), which cleave and degrade BP180, thus leading to subepidermal blister formation.[17] de Graauw et al.[18] have shown in an *ex vivo* model that monocytes and neutrophils act synergistically in the formation of dermoepidermal blisters in BP. Riani et al.[19] have noted that monocytes play a role in BP pathogenesis by increasing MMP-9 synthesis via CXCL10 (chemoattractant molecule) with neutrophils. Tetracyclines, especially doxycycline, have MMP inhibitory properties.[20] Another study showed that CCL18 chemokine levels in serum and blister fluid of patients with BP were higher than those in the control group, and in vitro chemotaxis analysis demonstrated that CCL18 triggers the migration of peripheral blood mononuclear cells to BP blister fluid.[21] In BP, CD163+ M2 tissue macrophages detected in increased numbers in lesional skin are responsible for the production of specific chemokines that induce the polarization of helper T cell subgroups. Minocycline, a tetracycline-class antibiotic, reduces the production of CCL22, CCL24, CCL26, and CCL2 from M2 macrophages while not affecting CCL18. On the other hand, the production of CCL18 was found to decrease with dexamethasone and cyclosporine.[22]

Most patients with BP are elderly, often use multiple drugs, and have significant comorbidities such as neurological and cardiovascular diseases, malignancies, and diabetes, making the treatment of BP quite challenging. Systemic corticosteroids can improve symptoms but may lead to numerous side effects, especially with prolonged use, and can even increase mortality rates. There is a need for an alternative treatment that can rapidly alleviate symptoms and maintain long-term remission while avoiding or minimizing the side effects of systemic corticosteroids.[23] Studies have reported that tetracycline group antibiotics are safer and similar to systemic prednisolone therapy in controlling the disease.[7,9,24]

In our study, 60% of patients with BP treated with tetracycline-class antibiotics were still in remission, whereas 40% experienced relapse. A systematic meta-analysis involving 341 patients with pemphigoid found that 77.7% of 148 patients using tetracycline with topical steroids responded to the treatment, but 31.8% experienced relapse.[25] The fact that there were only a limited number of patients with moderate and severe disease in our study may have contributed to the difference in the treatment responses.

In our department, patients' drugs associated with pemphigoid are determined, and if possible, they are stopped or changed. The frequency of patients taking drugs associated with pemphigoid was significantly higher in the remission group than in the relapse group in our study. Molina et al.[26] reported that patients with pemphigoid who continued to use the triggering drug more frequently needed immunosuppressive agents to achieve clinical remission. They also had to use them for a longer period. Therefore, withdrawal of the drug may have allowed patients to achieve remission under tetracycline therapy in our study.

In our study, a significant decrease in eosinophil count and ELR was observed in patients treated with tetracycline-class antibiotics compared with pretreatment. Gehring et al.[27] suggested that tetracyclines may be effective in BP by inducing eosinophil apoptosis. In a study evaluating peripheral blood and tissue eosinophil counts in BP patients, high eosinophil counts were associated with relapses and the need for hospitalization. The study indicated that peripheral eosinophil count could be used to monitor treatment response and identify relapse risk early.[16] The significant decrease in eosinophil counts in patients in remission in our study supports these findings.

As a different finding, a significant decrease in peripheral blood monocyte count was observed in the group continuing in remission after tetracycline treatment in our study. The significant reduction in monocyte count in the remission group suggests that monocyte levels can be an indicator of disease activity and the formation of relapse in addition to eosinophil counts. It has been shown that high anti-BP180 ELISA autoantibody titers in monitoring disease activity in BP is a good indicator of relapse.[28] However, these tests are expensive and not readily available, limiting their routine use. Hematological parameters, which are quick, easily accessible, and inexpensive tests, are used as inflammation markers in many diseases.

In our study, a significant decrease in CRP levels was observed in the group continuing in remission compared with the baseline value. In contrast, no significant change was detected in the relapsed group. Similarly, Sahin et al.[29] have identified

a significant decrease in MPV, peripheral eosinophil count, ESR, and CRP levels during the remission phase compared with the active phase in patients with BP. However, that study did not specify which treatments patients received or whether they were still undergoing any treatment. CRP is an acute-phase protein synthesized in the liver following stimulation by various inflammatory cytokines, including IL-6, IL-1, and tumor necrosis factor (TNF).[30] In BP patients, serum levels of IL-6 and TNF were found to be higher than those in the control group and correlated with lesion numbers and CRP levels.[31]

In our study, no significant statistical difference was observed when comparing the remission likelihood ratios between the tetracycline and doxycycline treatment groups. Systematic meta-analysis data showed that the patient response rate to tetracycline was statistically higher than that to doxycycline and minocycline.[25]

Study limitations

The limitations of our study include a small sample size, lack of a control group, its retrospective nature, and the fact that all subjects were from a single center. It was not possible to evaluate the efficacy of tetracycline therapy alone because patients received topical potent corticosteroid therapy in combination with tetracycline-class antibiotics. Anti-BP180 and anti-BP230 ELISA autoantibodies were not studied in patients with BP. Despite these limitations, our study has identified for the first time that peripheral blood monocyte counts are higher in patients with BP than in the healthy age- and gender-matched control group and significantly decrease in the group continuing in remission after treatment.

Conclusion

In conclusion, in patients with BP, peripheral blood monocyte and eosinophil counts were higher than the average/median of the healthy control group. After treatment with tetracyclines, a significant decrease in eosinophil and monocyte counts and CRP levels was observed only in the remission group. The frequency of previous drug use associated with pemphigoid was higher in the remission group than in the relapse group, indicating that withdrawal of these drugs is necessary for disease control. Tetracycline-class antibiotics are preferred in BP treatment because of their lower frequency of side effects and anti-inflammatory properties. Peripheral eosinophil count, ELR, and monocyte count, along with CRP, could serve as markers for monitoring the response to tetracyclines and the risk of relapse in patients with BP. Further studies with a larger patient series and control groups are needed to confirm these results and evaluate responses to other treatments.

Ethics

Ethics Committee Approval: Clinical data were evaluated after the approval of the Dokuz Eylül University Non-interventional Research Ethics Committee (approval number: 2022/42-01, date: 28.12.2022).

Informed Consent: Because of the retrospective nature of the study, informed consent of the patients was not required.

Authorship Contributions

Concept: C.A., Ö.G., S.A., Ş.A., Design: C.A., Ö.G., S.A., Ş.A., Data Collection or Processing: C.A., Ö.G., S.A., Ş.A., Analysis or Interpretation: C.A., Ö.G., S.A., Ş.A., Literature Search: C.A., Ö.G., S.A., Ş.A., Writing: C.A., Ö.G., S.A., Ş.A.

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