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PROFILE OF PERIPHERAL BLOOD CELL INFLAMMATORY INDICES IN HEMOPHILIA A PATIENTS ON INHIBITOR THERAPY

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ABSTRACT

Objective: The present study was designed to investigate the effect of Emicizumab on the peripheral blood cell systemic inflammatory markers of haemophilia A patients with inhibitors. **Materials and Methods:** This was a quasi-experimental study involving 16 Haemophilia A patients with inhibitors and 16 apparently healthy-age and gender matched controls. Inhibitor screening and titer were determined by the Nijmegen-Bethesda Assay. 3mg/kg b.wt Emicizumab (Remicade, Schering-Plough, Medical Products Trade A.S., Istanbul, Turkey) were administered to the haemophilia A patients and haemogram counts for both subjects and controls were determined using automated hematology analyzer (Mindray 530 BC, China). Data was analyzed using statistical package for social science version 25 (IBM statistics Armok, NY, USA) and presented as mean ± SD with $p<0.05$ considered significant. **Results:** Patients showed significant increase in the parameters involving the Neutrophil/lymphocyte ratio (37±5.3), monocyte/lymphocyte ratio (33±3.4), platelet/lymphocyte ratio (38±8.6), basophil/monocyte ratio (5.6±1.5) and eosinophil/lymphocyte ratios (42.6±4.4) for the hemophilia A patients on Emicizumab therapy at week4 compared to the controls (14±2.9, 8.8±2.3, 13±2.5, 0.37±0.1, 2.6±1.4 respectively). However, there were no significant differences at the week 12 on continued Emicizumab therapy (13.7±2.8, 9.2±3.0, 12.6±2.0, 7.2±1.3, 0.45±1.3 respectively).**Conclusion**: Reduction in systemic inflammation may be a mechanism for control of bleeding in hemophilia on Emicizumab therapy.

KEYWORDS: Inhibitors, Haemophilia A, Peripheral Blood Inflammatory Indices, Therapy.

INTRODUCTION

Hemophilia disease is a group of inherited bleeding disorders estimated to affect 1,125000 patients globally with 418000 having severe form of the disease.[1] It can be classified into hemophilia A, hemophila B and hemophilia C based on the coagulation factor that is deficient which could be FV111, FIX, FX1 respectively and occurs primarily in males.[2,3]

Inflammatory reactions contribute to changes in coagulation processes that exacerbate hemophilia. Systemic inflammatory in hemophilia have been implicated in various bleeding-related complications such as hemarthrosis and hemophilic arthropathy.[4,5] The current treatment to control such complications is prevention of recurrent bleeding episodes by prophylactic factor replacement.[6] Emicizumab is a humanized recombinant monoclonal antibody that mimics the function of coagulation factor V11.[7,8]

It has shown the capacity to bind simultaneously to activated factor IX and factor X thereby maintaining normal hemostasis.[9,10] Systemic inflammatory parameters such as neutrophil/lymphocyte ratio (NLR), Platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR), have been proposed as reliable markers of inflammation by many studies.[11,12] These ratios from the white blood cell and platelet count parameters obtained from the routine full blood count have shown to important meaningful markers of inflammation since changes in the balance proportions of their components indicates inflammation better than one single parameter. The NLR, MLR, ELR, PLR and BLR ratios have been predominantly applied as biomarkers of inflammation in variety of inflammatory conditions.[13,14] Despite being nonspecific, these ratios can guide treatment decisions and monitor effectiveness of treatment over time, predicting disease progression and risk of complications. The present study was therefore conducted to determine the effective of factor replacement therapy on the systemic inflammatory ratios in hemophilia A patients on Emicizumab therapy.

PATIENTS AND METHODS

This study was conducted at the University of Nigeria Teaching Hospital, Enugu State, Nigeria. The hospital is one of the teaching hospitals established by the Federal Government of Nigeria. It is situated in Ituku/Ozalla, about 20 kilometers from Enugu metropolis, and offers healthcare services to the five states of the South East Nigeria and neighboring zones. The ethical approval for the study was obtained from the Hospital Research Ethics Committee with approval number: UNTH/HREC/2025/02/4074 and informed consent was obtained from all subjects before the commencement of the study. It was a quasi-experimental study involving haemophilia A patients with inhibitors on Emicizumab (n=16) compared to healthy-age and gender matched individuals (n=16) with no family history or clinical evidence of haemophilia or any chronic diseases or obvious abnormalities taken as control subjects. Venous blood (4ml) was collected aseptically with 70% cotton swab from the antecubital fossa using standard procedure from each subject for inhibitor screening and inhibitor titer determination using the Bethesda Assay and then for the analysis of the full blood count parameters using the Mindray BC-530, automated analyzer. The Full Blood Counts of the subjects were tested after 4 weeks, 8 weeks and 12 weeks of taking Emicizumab 3mg/kg b.wt and compared with the control. The results were analyzed using Statistical Package for the Social Sciences (IBM, Statistics, Armonk, NY, USA) version 25.0 program. The differences in the complete blood count parameters of the control and tests groups over the 4^{th}, 8^{th} and 12^{th} weeks on Emicizumab were determined by one way analysis of variance. Differences between groups were considered significant at p- value less than or equal to 0.05 ($p<0.05$).

RESULTS

Table 1: Some Peripheral Blood Cell Inflammatory Indices among the study groups.

Parameter/Duration of Therapy	(Control)	4Week	8Week	12Week
NLR	14 ± 2.9	37 ± 5.3^{ab}	29 ± 3.5^{a}	13.7 ± 2.8^{b}
ELR	8.8 ± 2.3	42.6 ± 4.4^{ab}	34 ± 2.6^{a}	9.2 ± 3.0^{b}
MLR	13 ± 2.5	33 ± 3.4^{ab}	26.2 ± 3.7^{a}	12.6 ± 2.0^{b}
BLR	0.37 ± 0.1	5.6 ± 1.5^{a}	2.8 ± 1.9^{a}	0.45 ± 1.3^{b}
PLR	7.2 ± 1.3	38 ± 8.6^{a}	23.4 ± 3.9^{a}	7.8 ± 2.5^{b}

Data are presented as mean± SD; mean values having the lowercase alphabet "a" as superscripts are considered significant ($p<0.05$) compared to the controls while those having "b" are considered non-significant ($p>0.05$) compared to the controls. SD-Standard deviation, NLR – Neutrophil to Lymphocyte Ratio, MLR – Monocyte to Lymphocyte Ratio, Eosinophil to Lymphocyte Ratio, Basophil to Lymphocyte Ratio, PLR- Platelet to Lymphocyte Ratio.

The results of the peripheral blood cell systemic inflammatory indices among the study groups as shown (table 1) revealed no significant differences in the neutrophil lymphocyte ratio, monocyte lymphocyte ratio, eosinophil lymphocyte ratio and the basophil lymphocyte ratio for the hemophilia A patients with inhibitors on therapy for 12weeks compared to the controls. However, there was a non-significant increase in the neutrophil lymphocyte ratio, monocyte lymphocyte ratio, eosinophil lymphocyte ratio, and basophil lymphocyte ratio for the hemophilia A patients with Inhibitors on inhibitor therapy for 8weeks compared to the controls. For the hemophilia A patients on inhibitor therapy for only 4week, the result revealed a significant increase ($p<0.05$) in the neutrophil lymphocyte ratio, monocyte lymphocyte ratio, eosinophil lymphocyte ratio and basophil lymphocyte ratio compared to the controls.

DISCUSSION

The present study was conducted to determine the effect of Emicizumab therapy on the systemic inflammatory blood indices in hemophilia A patients with inhibitors. From the results of this study, it was observed after 4 weeks of Emicizumab (3mg/kgb.wt.) administration that there was a significant increase in the neutrophil/lymphocytes ratio, monocyte/lymphocyte ratio, platelet/lymphocyte ratio and the eosinophil/lymphocyte ratio for the hemophilia A patients compared to the controls. The increase in lymphocytes could be attributed to the presence of

antibodies against the FVIII replacement therapy which usually will reduce in titre gradually as antibodies takes some time in the body before being cleared, an increase in regulatory B & T cells is crucial in maintaining immune tolerance to by -passing agents as recorded in some other study.[15]

The results after week 8 of Emicizumab administration revealed non-significant increase in the parameters for the hemophilia patients compared to the control. This could be attributed to an increase in regulatory B and T lymphocytes creating an immune tolerance to the drug and a compensatory mechanism to create a physiological equilibrium for the better functioning of the body.[16]

The results of 12 weeks after the administration of Emicizumab (3mg/kgb.wt.) showed no significant differences in the parameters for the hemophilia A patients compared to the control. This findings suggests that symptoms of inflammation in hemophilia patients such as the recorded deregulated systemic inflammatory blood cell ratios by hemophiliacs represents a recurrent inflammatory stimulus.[17] The limitations in the present study are the small sample size owing to the number of patients available during the study period and the cross-sectional design which did not allow us to follow-up patients for a longer period.

CONCLUSION

Emicizumab normalizes the values of systemic blood cell inflammatory markers in hemophilia A patients with inhibitors. Thus, amelioration of systemic inflammation in patients might be a mechanism for control of bleeding and its associated complications in these patients.

Declarations

Ethical Approval: Approved.

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Conflict of Interest: Author Declare no competing interest.

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