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USE OF RITUXIMAB IN THE TREATMENT OF REFRACTORY NON-INFECTIOUS UVEITIS

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ABSTRACT

Background: Uveitis is an inflammatory eye disease causing 30,000 new cases of legal blindness annually in the USA. It can be idiopathic, systemic, viral, inflammatory, or traumatic. Infectious causes account for 20% of cases. Treatments include corticosteroids, non-corticosteroid immunosuppressive agents, leukocyte inhibitors, and alkylating agents. **Aim:** To evaluate the effect of the Rituximab in the treatment of refractory Uveitis. **Patients and Methods:** A study involving 106 refractory Uveitis patients at the Specialized Center of Ophthalmology in Mosul from February 2022 to February 2024 evaluated their condition, prescribed Rituximab, and analyzed statistically using SPSS-26. **Results:** The study involved 106 patients aged 40-80 years, with a female-dominated distribution of 67.9% and a male-dominated 32.1%. The majority had posterior Uveitis, with 27 patients having Non-paraneoplastic autoimmune Retinopathy, 19 patients having juvenile idiopatic arthritis, 11 patients having cancer-associated and Melanoma-associated retinopathy, and 10 patients having Behcet's disease. Out of 106 patients, 78.3% had a positive response to Rituximab, with significant differences in underlying conditions. Recurrence was reported in 19.8% of patients. **Conclusion:** Most patients experienced a clinical remission of inflammation after taking rituximab, which demonstrated an efficacious response to therapy. For those who are not responding to conventional treatments, it may be a lifesaver.

KEYWORDS: Refractory, Rituximab, Uveitis.

INTRODUCTION

The uveal layer of the eye is affected by the potentially blinding inflammatory illness known as uveitis. In the USA, it's thought to be the cause of 30,000 new cases of legal blindness each year.[1]

Thirty percent of instances of uveitis are idiopathic, meaning their cause is unknown. In contrast, non-infectious uveitis—which is more prevalent in industrialized nations than infectious uveitis—is thought to be caused by an underlying systemic disease in 25 to 50% of cases.[2,3] But viral, inflammatory, and traumatic causes have also been connected to it. Patients may have concurrent systemic symptoms or infectious illnesses, which would suggest a multisystemic etiology. 48 to 70% of cases of uveitis are idiopathic.[4]

Behcet's disease (BD), juvenile idiopathic arthritis, sarcoidosis, tubulo-interstitial nephritis (TINU), and HLA-B27-associated entities are among the systemic inflammatory illnesses that are frequently linked to anterior uveitis. While Vogt-Koyanagi-Harada syndrome, leukemia, lupus, BD, and multiple sclerosis can induce a posterior uveitis with systemic signs, sarcoidosis, TINU, and multiple sclerosis are the causes of intermediate uveitis with systemic manifestations. Pan-uveitis is another possible symptom of BD, a systemic vasculitis.[5] About 20% of instances of uveitis are assumed to be caused by infectious processes, while the underlying reasons might differ regionally.[6] Viral infections (HSV, VZV, CMV), bacterial infections (endophthalmitis, syphilis, TB, etc.), and parasitic or worm infections (toxoplasmosis, Lyme disease, toxocara, *Bartonella sp*., or other unusual diseases) are examples of infectious causes.[7,8]

For non-infectious uveitis and scleritis, corticosteroids are the main therapy, although their long-term usage is constrained by adverse effects. Alkylating agents, leukocyte inhibitors, and non-corticosteroid immunosuppressive drugs are examples of conventional therapies. Humanized anti-CD20 antibody rituximab is

being utilized more often to treat ocular inflammation that is resistant to these treatments.[9] The current study aimed to evaluate the effect of the Rituximab in the treatment of refractory Uveitis.

PATIENTS AND METHODS

A prospective study was conducted on 106 patients who were diagnosed to have Uveitis that refractory to traditional treatments who attended Specialized Center of Ophthalmology in Mosul city from February 2022 to February 2024. The convenient sampling technique was used to collect the patients and they were evaluated, examined, and followed by the researchers. The Rituximab was prescribed for these patients, and their condition was re-assessed in each visit. The data was analyzed statistically by SPSS-26.

RESULTS

The study included 106 patients with age ranged from 40 to 80 years. The distribution according to sex showed predominance of the female gender that prevailed among 67.9% while the males represented 32.1%, the male to female ratio was 0.48:1 as shown in figure (1).

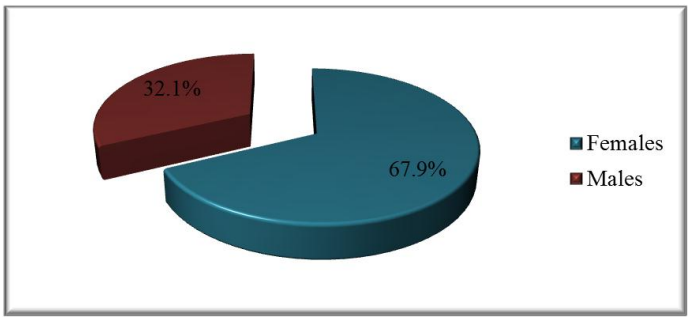


Figure 1: Distribution of the cases according to sex.

Distribution of the cases according to types of Uveitis was demonstrated in figure (2). This figure illustrated that 56 patients had posterior Uveitis, 31 patients had anterior Uveitis, and 14 patients had pan Uveitis.

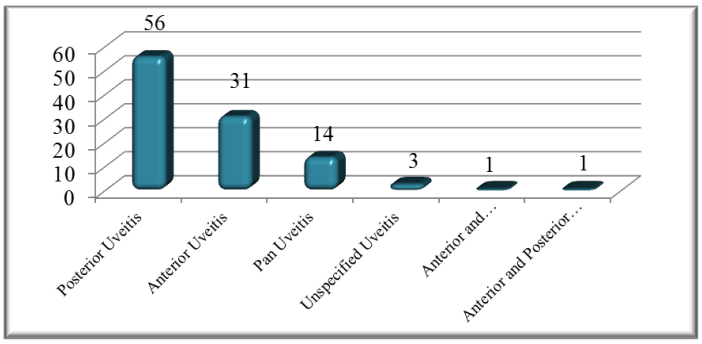


Figure 2: Distribution of the cases according to types.

The identified cause of Uveitis was showed in table (1) which revealed that 27 patients had Non-paraneoplastic autoimmune Retinpathy, their age ranged from 50-66 years and all were posterior Uveitis. Juvenile idiopatic arthritis was found among 19 patients with younger age of 20-27 years, all were anterior Uveitis. Cancer associated and Melanoma associated retinopathy was reported in 11 patients who were older than the other with age ranged 50-80 with posterior Uveitis. Behcet's disease found in 10 patients, Vogt koyanagi harada syndrome in 9 patients and Sarcoidosis only in 4 patients. Only Behcet's disease showed predominance of males gender.

Table (1): Distribution of the Uveitis according to the identified causes.

Identified cause of Uveitis	No. (%)	Age (years)	Sex ratio	Anatomical localization
Non-paraneoplastic autoimmune Retinpathy	27	50-66	0.4:1	Posterior Uveitis
Juvenile idiopatic arthritis	19	20-27	0.2:1	Anterior Uveitis
Behcet's disease	10	19-40	1.8:1	Posterior Uveitis Anterior Uveitis
Vogt koyanagi harada syndrome	9	14-35	100.0% females	7 anterior Uveitis 2 pan-uveitis
Cancer associated and Melanoma	11	50-80	0.4:1	Posterior Uveitis

associated retinopathy				
Sarcoidosis	4	46-50	0.43:1	Posterior Uveitis
Idiopathic	17	30-50	0.22:1	Posterior Uveitis
Intermediate Uveitis	9	45-65	0.41:1	Anterior Uveitis

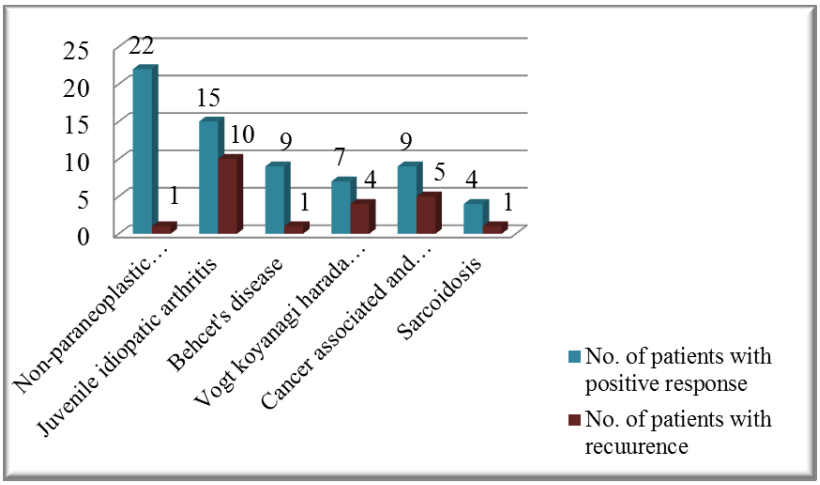
Positive response to Rituximab according to underlying conditions was demonstrated in table (2) which showed that 83 patients out of 106 had positive response representing 78.3% that distributed according to different underlying conditions showing statistically significant difference for Non-paraneoplastic autoimmune Retinpathy, Juvenile idiopatic arthritis, Behcet's disease, and Cancer & Melanoma associated retinopathy.

Table 2: Positive response to Rituximab according to underlying conditions.

	Positive response	**No response**	**p-value***
	No. (%)	**No. (%)**	
Non-paraneoplastic autoimmune Retinpathy	22	5	**0.001**
Juvenile idiopatic arthritis	15	4	**0.012**
Behcet's disease	9	1	**0.011**
Vogt koyanagi harada syndrome	7	2	0.096
Cancer & Melanoma associated retinopathy	9	2	**0.035**
Sarcoidosis	3	1	0.317
Idiopathic	12	5	0.090
Intermediate Uveitis	6	3	0.317

**Chi square for goodness of fit*

The recurrence was reported in 21 patients out of the 106 under the study represented 19.8%, distributed as shown in figure (3).



DISCUSSION

Ocular inflammatory disorders, intraocular lymphoma, and autoimmune illnesses have all been effectively treated with rituximab, an IgG antibody that targets CD-20. Additionally, it has shown effective in the treatment of scleritis.[10]

The age range of uveitis patients was 40–80 years, in line with the findings of González *et al.*[11] who observed that the mean patient age was 53 ± 13 years.

According to the current study, patients with uveitis are predominantly female. Previous research has demonstrated that women are more likely than males to experience ocular inflammatory diseases, especially in women who are reproductive age, and that this gender difference grows as women age.[12] It is believed that sex hormones and women's additional X chromosome contribute significantly to the development of these immune-mediated illnesses.[12,13] While studies conducted in a number of wealthy countries have revealed this gender difference[14,15], emerging nations like Turkey and India have discovered a reverse gender bias, with a male preponderance.[16,19]

This research found that 78.3% of patients with refractory uveitis responded well to treatment with rituximab. Rituximab has been found to be just as effective as cyclophosphamide in the therapy of ocular GPA, according to the Ahmed and Foster trial.[20]

According to Onal *et al.*[21] and some cases of scleritis, the response to rituximab treatment may be variable, particularly in cases with granulomatous manifestations of ANCA-associated vasculitis (such as orbital inflammation) and may require a shorter time to remission. It is believed that B cell-produced ANCA mediates scleral inflammation in GPA. This is why rituximab aids in the treatment of scleritis by depleting B cells. But aside from ANCA-associated scleritis, rituximab has also been shown to be effective in treating scleritis resulting from RA and a number of other autoimmune illnesses, as described in a research by Suhler *et al.*[22]

According to Cao *et al.*[23] there were 15 patients and a mean follow-up of 34 months. At six months, 13 (86.6%) of the 14 patients (93.3%) who had demonstrated a clinical improvement had a scleritis activity score of zero. According to a research by Jakob *et al.*[24] six individuals had Wegener disease (4 orbital granulomatosis, 1 Tolosa-Hunt syndrome, and 1 scleritis); one patient had intermediate uveitis and scleritis as a result of Behçet illness; and two patients (RA and JIA) had iridocyclitis. Over a mean follow-up of 19 months, patients underwent a mean of 4 infusions. The level of ocular inflammation improved or stabilized in all of the individuals. Four individuals had improved BCVA, and the remaining four had maintained BCVA. The European League of Arthritis and Rheumatism (EULAR) reports that one patient responded to therapy, and eight patients were in remission. Corticosteroids less than 7.5 mg and immunosuppressive treatment might be tapered for 8 individuals.

The participants who took part in the current study reported the negative effects. Only one side event (infusion hypotension) necessitated stopping rituximab in the Cao *et al.*[23], whereas no major side effects were observed in the Ma *et al.*[25], patients receiving this medication.

Recurrence was observed in 19.8% of the present cohort, which was comparable to rituximab recurrences, particularly in studies with extended follow-up periods.[22,23,26] Most of these instances improved with the same medication used for retreatment.[26] In terms of safety and effectiveness, rituximab seems to be a better option than cyclophosphamide.[20] Stilling-Vinther and Pedersen[27] described a case of posterior scleritis in an 81-year-old man with several comorbidities who died after receiving rituximab therapy for Pneumocystis Jirovecii pneumonia. Reports of cystoid macular edema have been made after rituximab therapy for scleritis was effective.[28] Retrospective research data revealed that 16% of individuals had secondary infections, with 8% necessitating hospitalization.[22]

CONCLUSION

Most patients experienced a clinical remission of inflammation after taking rituximab, which demonstrated an efficacious response to therapy. For those who are not responding to conventional treatments, it may be a lifesaver.

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