Original Article

Biological therapy in refractory cases of uveitis and scleritis: An analysis of 18 cases from a tertiary eye care center from South India

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Purpose: To evaluate the effectiveness of biologic therapy in a cohort of patients with various types of refractory non-infectious uveitis and scleritis. **Methods:** A retrospective observational study on patients with non-infectious uveitis and scleritis who were not responding or had a high recurrence rate with the conventional treatment and had received biologic therapy. **Results:** We studied 18 patients (33 eyes) who received biological therapy between January 2017 and November 2019. The mean age was 30 ± 17 years and mean duration of uveitis was 36.8 months (range 1–120 months). Anterior uveitis (27.7%) was most commonly observed followed by scleritis, panuveitis, posterior, and intermediate uveitis. The most common etiology was Behçet's disease (4 patients, 22.2%) followed by juvenile idiopathic arthritis (3 patients, 16.6%), granulamotosis polyangitis, and idiopathic (2 patients each, 11.1%). Majority had trialled one or more immunosuppressive and were refractory in nature. Maximum patients had received adalimumab (61%) followed by infliximab (22%), rituximab (12%), and golimumab (6%). The median prednisolone dose was reduced from 30 mg (range 7.5–60 mg) to 5 mg (range 0–10 mg) after biological therapy (P = 0.002). Significant visual improvement was observed post biologic therapy (mean log mar VA 0.41 ± 0.62 improved to 0.23 ± 0.48 at the final visit, P = 0.008). Maximum number of patients (16 patients, 89%) responded well with biological therapy. Three patients developed recurrence and systemic complications were observed in two patients. **Conclusion:** Biologic therapy is effective in non-infectious refractory uveitis who were resistant to conventional therapy and may prolong disease recurrence.

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Uveitis, the inflammation of the uveal tract accounts for about 10–25% of legal blindness in developing countries.[1] Despite of having various formulations of corticosteroid and numerous systemic immunosuppressive agents, effective and long-term control of intraocular inflammation remains a major challenge. Drug-related side-effects, resistance to therapy, and recurrence of the inflammation can pose significant obstacle in the management of uveitis with conventional therapies. Biologicals especially monoclonal antibodies have emerged out as a useful alternative for difficult-to-treat cases and treatment-resistant cases of uveitis. Many of these agents, approved for treating systemic rheumatic diseases, were successfully translated into ophthalmic practice for treating uveitis in recent years.[2,3] However, the literature from India on the use of biologicals in uveitis remains sparse. The present study highlights the use of biologicals in patients with refractory cases of uveitis and scleritis in a tertiary eye care center from South India.

Methods

The current study was a hospital-based retrospective, interventional case series that reviewed the data of all refractory cases of uveitis and scleritis, who received treatment with biological agents from January 2017 to November 2019. All patients included in the index study were referred to our institute as they were refractory to the treatment provided elsewhere. The study was approved by the institutional review board of the hospital and adhered to the Declaration of Helsinki. A case of scleritis/uveitis was defined as refractory, when there was a relapse within 3 months despite of receiving corticosteroids (10 mg/day or more) as maintenance therapy and/or with one or more immunosuppressive (s).

A detailed medical as well as ophthalmic history was elaborated in each patient when they visited us. History of Koch's contact was stressed and asked for in each patient. For every patient, information was gathered regarding demographic details as well as laterality, course, and concomitant systemic diseases. Furthermore, numbers of topical drugs used for treating inflammation, as well as systemic and regional corticosteroids and immunosuppressive drugs, were recorded. In all the patients, best-corrected visual acuity (BCVA), intraocular pressure measurement using Goldmann applanation tonometry, slit-lamp examination,

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and indirect ophthalmoscopy were performed at baseline and all follow-up visits. All the patients in the study underwent a thorough scrutiny to cross-check the laboratory investigations done before arriving at a diagnosis and subsequent treatment. Additional investigations were advised wherever deemed necessary. The laboratory investigations performed in these patients included a complete blood count, C-reactive protein, HLA B27, anti-nuclear antibody, Mantoux test, High-resolution chest computed tomography (HRCT chest), serologies for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV) and syphilis. Patients with scleritis underwent additional tests such as anti-nuclear cytoplasmic antibody (ANCA). When necessary, the examination included optical coherence tomography, fluorescein angiography, indocyanine angiography, and ultrasound B scan. In presence of anterior chamber reaction, wherever an infectious etiology was suspected, polymerase chain reaction from aqueous paracentesis was advised. The uveitis was classified as per the criteria of the Standardization of Uveitis Nomenclature Working Group (SUN) and standard diagnostic criteria were followed while confirming the diagnosis.[4]

All these patients were routinely evaluated by an in-house internist and opinion was sought from a pulmonologist in cases with clinical suspicion to rule out the diagnosis of tuberculosis and sarcoidosis. All cases were evaluated by a rheumatologist and a decision to start biological therapy was decided by the ophthalmologists in accordance with the rheumatologist. Patients with recurrent inflammations in spite of being oral immunosuppressive or oral corticosteroid with or without systemic involvement were the indications for initiation of biological therapy. All the patients were screened thoroughly and ruled out for active infection prior to administering biological therapy. The duration of therapy was decided by the rheumatologist in consultation with ophthalmologist.

A relapse was considered when a patient who was in remission experienced a new flare of uveitis and remission was defined as inactive disease for at least 3 months. BCVA results were converted to logarithm of the minimal angle of resolution (logMAR) for statistical analysis and are presented as logMAR.

Results

The study included 33 eyes of 18 patients who received biological therapy for the treatment of scleritis and uveitis. Four patients had scleritis and 14 patients had uveitis. Thirteen patients were male and mean age of these patients was 30 ± 17 years (range: 7–67 years). The cohort of scleritis patients included two patients with necrotizing scleritis, one patient of posterior scleritis, and diffuse anterior scleritis each. Among uveitis group, anterior uveitis [27.7%, two were HLA-B27 positive (Case12 and 17)] was the most common cause of uveitis followed by panuveitis (22.2%), posterior uveitis (16%). Behçet's disease (22.2%) was the most common cause of inflammation in the present study, followed by juvenile idiopathic arthritis (16.6%), granulamotosis polyangitis, and idiopathic (each 11.1%). The demographic details and clinical profile of the patients in current study were highlighted in Table 1.

Table 1: Clinical Profile Patients With Uveitis And Scleritis

	Number (%)
Number of Patients (Eyes affected)	18 (33)
Bilaterality	15 (83%)
Mean Age (range)	31 (7-67)
Mean Follow-up in months (range)	18.5 (3-36)
Median duration of uveitis prior to Biologic initiation (range)	36 (1-120)
Etiological Diagnosis	
Behçet's Disease	4 (22.2%)
Juvenile Idiopathic Arthritis	3 (16.6%)
Granulomatous Polyangiitis	2(11.1%)
Idiopathic	2 (11.1%)
Crohn's Disease	1(5.5%)
Blau Syndrome	1(5.5%)
Inflammatory Bowel Disease	1(5.5%)
Ankylosing Spondylitis	1(5.5%)
Rheumatoid Arthritis	1(5.5%)
Vogt Koyanagi Harada Syndrome	1(5.5%)
Psoriasis	1(5.5%)
Anatomical Diagnosis	
Anterior Uveitis	5 (27.7%)
Intermediate Uveitis	2 (11.1%)
Posterior Uveitis	3 (16.6%)
Panuveitis	4 (22.2%)
Scleritis	4 (22.2%)

Before switching over to biological therapy, these patients were on various immunosuppressive and oral corticosteroid prescribed elsewhere. Seven patients were on oral methotrexate (15 mg/week or more), five on mycophenolate mofetil (1,000 mg 2 times daily), and three patients were on oral azathioprine (50 mg three times daily). Four patients were on two immunosuppressives before planning biological therapy. Median duration between diagnosis of uveitis and immunosuppressive therapy before planning biologicals was 36.8 months (Range: 1–120 months). Eleven patients (61%) received adalimumab in the current study and four patients (22%) were treated with infliximab. Two patients (11%) were treated with rituximab and golimumab was administered in one patient (6%) [Table 2]. Median duration of biologic therapy was 12.7 month (range 3–36 months). One patient with psoriasis receiving infliximab developed miliary tuberculosis after tenth dose of the drug. The treatment with infliximab was immediately stopped and the patient was started on anti-tuberculosis treatment under the supervision of a chest physician. There was persistent retinal vasculitis, which subsides on starting oral prednisolone. The patient developed glaucoma and was on anti-glaucoma medications while maintaining a 6/6 visual acuity in both eyes at the final visit. One patient with Blau syndrome was switched over to adalimumab from infliximab, as developed systemic hypertension.

Three patients in the current study developed recurrence; two patients who had received biologicals for a period of 12 months developed recurrence of inflammation 6 months after discontinuation of biological therapy. Among these two patients, recurrence in the form of anterior uveitis in patient with JIA (Patient 1) was treated with topical and cycloplegic and he was maintained on oral corticosteroids 5 mg/day.

Table 2: Details of the patients

Pt. No	Age/Sex	Aetiology	Ocular manifestations	Previous Treatment	Biologic	Medications along with Biologic
1	7/F	JIA	Bilateral Anterior uveitis	MTX,PRED	Adalimumab	MTX
2	30/M	JIA	Bilateral Intermediate uveitis	PRED	Infliximab	PRED
3	14/M	JIA	Bilateral Anterior uveitis	MTX,PRED	Adalimumab	MTX
4	32/F	VKH	Bilateral Panuveitis	MTX , PRED,IVMP	Adalimumab	MTX
5	30/M	BD	Bilateral Panuveitis	PRED CsA AZA	Adalimumab	PRED,AZA
6	35/M	BD	Bilateral Posterior Uveitis	CsA ,PRED,MMF	Infliximab	PRED
7	27/M	BD	Bilateral Posterior Uveitis	AZA,PRED, CsA	Adalimumab	PRED, CsA
8	12/F	BD	Bilateral Panuveitis	AZA,PRED	Adalimumab	PRED
9	67/M	GPA	Bilateral Posterior Scleritis	MMF, PRED, CsA	Rituximab	PRED
10	41/F	GPA	Panuveitis	MMF,PRED	Rituximab	PRED
11	7/M	Blau syndrome	Bilateral Anterior Uveitis	PRED,MTX,	Infliximab Switched to Adalimumab	MTX
12	46/M	AS	Bilateral Anterior Uveitis (Alternating)	MTX,PRED	Infliximab	MTX
13	56/M	Idiopathic	Diffuse Scleritis	PRED,CPA	Adalimumab	PRED
14	33/M	Idiopathic	Bilateral Necrotising Scleritis	PRED,MMF	Adalimumab	PRED
15	28/M	IBD	Bilateral Intermediate uveitis	PRED, CsA, MMF,MTX,	Adalimumab switched to Golimumab	CsA
16	10/M	Crohn's disease	Bilateral Anterior Uveitis	MTX,PRED	Adalimumab	MTX
17	64/F	RA	Necrotizing scleritis	PRED,IVMP,	Adalimumab	PRED
18	36/M	Psoriasis	Bilateral Posterior Uveitis	PRED, CsA	Infliximab	PRED

(M=Male, F=Female, JIA=Juvenile idiopathic Arthritis, VKH= Vogt-Koyanagi-Harada Disease, BD= Behçet's Disease, GPA= Granulomatosis with polyangiitis, AS= Ankylosing Spondylitis, IBD= Inflammatory Bowel Disease, RA= Rheumatoid Arthritis, MTX= Methotrexate, PRED= Prednisolone, IVMP= Intravenous methylprednisolone, CsA = Cyclosporine, AZA =Azathioprine, MMF = Mycophenolate mofetil, CPA= Cyclophosphamide

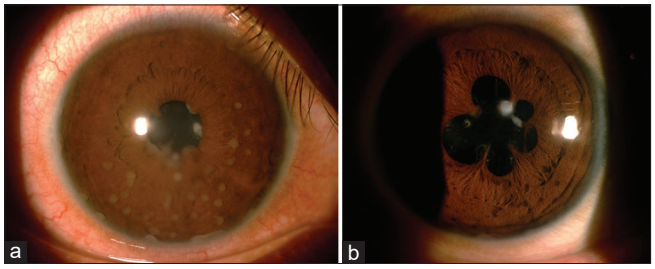

Figure 1: A 8-year-old boy with Blau syndrome had recurrent anterior uveitis with conventional treatment, at presentation he was having bilateral anterior uveitis 3+ and iris nodules. At 3 month follow-up after starting biologics he showed significant improvement in clinical activity and at 6 months there was no evidence of inflammation and Iris nodules

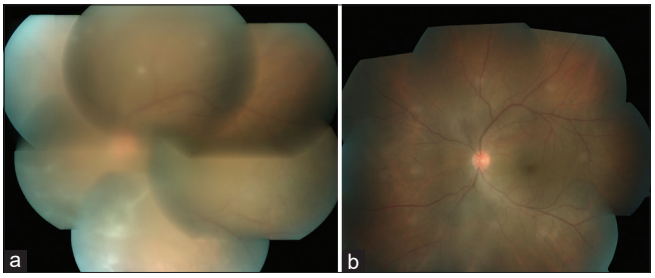

Figure 2: A 30-year-old male with bilateral panuveitis associated with Behcet's disease presented with active bilateral panuveitis and severe vitritis was started on adalimumab showed significant reducation of vitritis and other clinical parameters within 6 weeks

Recurrence in other patient (Patient 4) with VKH was treated with pulse corticosteroid followed by high doses of oral steroids (1 mg/kg of body weight) and oral methotrexate (15 mg weekly). The third patient (Patient 15) developed recurrence of inflammation while on adalimumab and was subsequently shifted to golimumab by the rheumatologist.

The median dose of corticosteroid prior to biological therapy was 30 mg (range 7.5–60 mg) which could be reduced to 5 mg (range 0–10 mg) with the biological therapy ($P = 0.002$, Wilcoxon signed rank test). The study observed systemic complications in two patients following biological therapy. One patient with Blau syndrome had developed secondary hypertension after infliximab [Fig. 1]. The other patient with psoriasis developed milliary tuberculosis post multiple infliximab infusions before presenting to our clinic. The most common ocular complication was glaucoma (3 patients, 16.6%,) followed by cataract (2 patients, 11.1%); however, none of these patients required any surgical intervention. Before initiation of biologic therapy the mean (SD) log mar visual acuity was 0.41 ± 0.62 which improved to 0.23 ± 0.48 at the final visit ($P = 0.008$, Wilcoxon signed rank test) Through the follow-up most of the eyes maintained a stable visual acuity, nine eyes showed improvement in BCVA and 22 eyes had a maintained visual acuity.

Discussion

There are growing evidences on the efficacy of the various biological agents in the management of treatment-resistant cases of uveitis in last few decades. However, there is a sparsity of literature on the use of biological therapy in the treatment of uveitis from India. This retrospective case series highlighted the efficacious use of four such agents—infliximab, rituximab, adalimumab, and golimumab in management of treatment-resistant cases of uveitis and scleritis. Infliximab, adalimumab, and golimumab are examples of tumor necrosis factor (TNF)-α blockers and rituximab acts by inhibiting CD-20, a B cell surface antigen. Infliximab is a chimeric monoclonal antibody whereas rituximab is a human–mouse chimeric monoclonal antibody. Both infliximab and rituximab is administered by intravenous route. Adalimumab and golimumab are human monoclonal antibodies which can be administered subcutaneously. Human monoclonal antibodies are significantly less immunogenic products with improved *in vivo* tolerability. In the current study we did not observe any significant tolerance issue such as infusion reaction with infliximab. One of the patients on infliximab developed systemic hypertension and was switched over to adalimumab. Systemic hypertension secondary to infliximab is not very common, but has been reported in literature.[5]

Adalimumab is the first FDA approved drug for the management of non-infectious uveitis.[6] Majority of the patients (61%) in the current study received adalimumab including three patients with JIA. In a prospective clinical series of 39 children and adolescents with treatment resistant-JIA-associated uveitis, Adalimumab has been found to be well-tolerated with a recurrence rate of 7.8%.[7] In index study all the three patients who had recurrence following biological therapy were on adalimumab. In one patient, switching over to golimumab was useful and we did not observe further recurrences with the use of the drug [Fig. 2]. All of our patients with Behçet's disease showed clinical improvement and were able to maintain quiescence post 6 months of follow-up. Inappropriate regulation of TNF-α has been implicated to play a key role in the pathogenesis of Behçet's disease.[8] Thus blocking of TNF-α may help in the management of the disease. Recently a retrospective study on Behçet's disease patients from Turkey reported that 41% patients failed to respond to standard immunosuppressive therapy. Thus, it is crucial to consider biological therapy in patients with Behçet's disease who fails to respond to immunosuppressive therapy.[9] TNF-α blockers especially infliximab and adalimumab have been used widely in the successful management of Behçet's disease.[10]

In accordance with the literature, rituximab was found to be efficacious in the management of ophthalmic manifestation of GPA in the current study. Two of our patients with GPA responded well to the drug. There has been a growing evidence on the efficacious use of rituximab in the management of scleritis especially in patients with GPA.[11] Rituximab exerts its primary function by depletion of B lymphocytes. This may be the reason inflammation mediated by ANCA which in turn produced by B cells, responds well to rituximab.

As TNF-α blockers target one of the central defense system of the immune system, risk of secondary infection especially tuberculosis remains high with the use of these agents.[12] One of our patients developed milliary tuberculosis following multiple infliximab infusions. Thus, TNF-α blockers should be used with caution in tuberculosis endemic country like us. The ophthalmologists need to discuss the risk-benefit aspect of biological therapy, explain the probable side-effects of the therapy, and pursue the patients for close and regular monitoring. In current study the median dose of corticosteroid could be reduced from 30 mg to 5 mg with biological therapy. This indicates an important aspect in patients with chronic inflammation where a long-term immunosuppression is required and in children to reduce the corticosteroid related deleterious side-effects on growth and bone metabolism.

This case series is a retrospective review and has, therefore, limitations. The current study typically involved difficult-to-treat, severe diseases with delayed presentation. We had only a limited number of patients from various types of inflammation, making it difficult to interpret the efficacy of four different biological agents in the current study. However, considering the lack of literature on the use of biologicals from India, we believe the observation from this study may be of clinical interest for the Indian ophthalmologists.

Conclusion

To conclude, biologicals can be a useful alternative for the management of uveitis and scleritis cases resistant to standardized immunosuppression. In tuberculosis endemic country, these agents should be used with utmost caution. Both TNF-α blockers and CD-20 inhibitor can be efficacious to provide longer-lasting local disease control in patients with uveitis and scleritis. Future multi-center studies with a large sample size can be helpful in determining effective therapeutic approaches with these agents and can specifically address the safety of these agents in India.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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