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REVIEWS

Biologics in uveitis: An update

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Abstract

'Uveitis is' the term used to describe inflammation of the uvea. It can be due to infective or non-infective agents. Most of the non-infectious uveitides are autoimmune or auto-inflammatory in nature, and the management of non-infective uveitis is often crucial. Advancements in biotechnology and understanding the pathophysiologies of autoimmune diseases have enabled the development of the new class of drugs named 'biologics'. These drugs act at cellular level inhibiting the actions of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1, and IL-6, and B and T lymphocytes. Biologics have been proven to be less toxic and can be used in uveitic cases that are refractory to conventional therapy. Though the efficacy of biologics is based on insufficient clinical trials, majority of them indicate preferable outcomes on refractory uveitis, with remarkable promise to increase the possibility of long-term remission. In this review, we aimed to outline the ideal characteristics of each biologic drug and review the data to support the use of current and emerging biological therapies.

Keywords: Biologics, uveitis, cytokines, anti-TNF alpha, management

Introductıon

Uveitis is a broad term to describe the inflammation of vascular coat of the eyeball. Anatomically, it can be classified as anterior, intermediate, posterior, and panuveitis (where all the layers of uvea are involved).[1] The prevalence of uveitis ranges from 38-284/100,000 in adults, but it is significantly lesser in children (28/100,000).[2] Despite the rarity, uveitis is the cause for legal visual impairment in about one third of the population.[3, 4]

Uveitis can be due to infectious agent or underlying systemic disease. In some cases, the underlying cause is not detected even after tailored laboratory investigations, and they are categorized as 'idiopathic'.[5] The first choice of treatment in idiopathic uveitis is corticosteroids.[6] Long-term use of corticosteroids produced toxic effects both locally and systemically.[6,7] Corticosteroid-sparing immunomodulatory treatments were subsequently introduced to avoid such side effects. However, these therapies did not lead to suffice outcomes in some active uveitis cases or in the management of adverse effects.[8] In order to circumvent this limitation, a new choice of drug named 'biologics' has been derived from living microorganisms, plants or animal cells.[7] These agents target immune and inflammatory pathways at the cellular level thereby suppressing immune response and preventing further structural damage.[9] Based on the target receptor, biologics can be classified into the following categories (Table 1):

1. TNF-α inhibitors
2. Anti-interleukin therapies
3. Interferons
4. Fusion protein of CTLA-4

1.TNF- α inhibitors

The cytokine TNF-α, a pro-inflammatory cytokine, plays a vital role in immune response to trauma or bacterial infections. TNF-α is produced by various cells including neutrophils and macrophages.[6, 10] Increased level of TNF-α is noted in many autoimmune diseases and ocular inflammatory conditions. Studies have found increased concentrations of membrane-bound TNF-α and soluble TNF-α in aqueous humour during the disease activity.[11-14] Therefore, numerous targets have been identified, which act against TNF-α for the potential management of inflammation.

Adalimumab

It is a fully humanized monoclonal antibody directed against

TNF- α. It has been approved by FDA for the management of non-infectious uveitis. The drug has been approved in many cases of non-infectious uveitis.[6, 8, 15] There are several studies suggesting the efficacy of adalimumab in the management of refractory uveitis. A multi-center study done by Jaffe *et al.* has found adalimumab to be associated with lowering uveitic inflammation and improving visual acuity in active non-infectious uveitis patients.[16] Nguyen *et al.* have reported prolonged remission time with marked visual improvement in non-infectious uveitis cases treated with adalimumab.[17] A study by Suhler *et al.* has noted that patients treated with adalimumab has sustained quiescence, without any increase in corticosteroid dose.[18] A prospective study intended to find the efficacy of adalimumab in active ankylosing spondylitis (AS)-associated uveitis has noted a reduction in anterior chamber flare by 51%.[19] Another study showed considerable amount of reduction in recurrences in AS-associated uveitis patients receiving adalimumab.[20] In sarcoidosis patients, complete resolution of papillitis and improvement of cystoid macular edema (CME) had been achieved.[21] Adalimumab showed significant improvement in visual acuity with the sustained remission of disease in a cohort with Bechet disease.[22] A multicenter placebo-controlled study showed significantly lesser treatment failure in adalimumab arm in JRA-associated uveitis cases.[23] Toxic effects of adalimumab should also be considered, despite its satisfactory results. The most common side effects are localized allergic reactions and headache. Severe side effects include malignancy, thrombolytic events, and congestive heart failure, and reactivation of tuberculosis (TB).[24]

Infliximab

Infliximab is a chimeric monoclonal antibody, which neutralizes both soluble- and membrane-bound TNF- α.[3,6] It has been proven to be effective in many non-uveitic conditions such as JIA-associated uveitis, sarcoidosis, birdshot chorioretinopathy, diffuse subretinal fibrosis, and sympathetic ophthalmia.[3,10] Suhler *et al.* have achieved clinical success in 18 out of 23 patients with Behcet's disease-associated uveitis.[25] Markomichelakis *et al.* have compared the efficacy of infliximab and triamcinolone in reducing ocular inflammation.[26] Better outcome results were noted in the group treated with infliximab, despite its side effects. In Japanese patients with Bechet's disease, there was improvement in disease status and mean visual acuity in 69%. However, half of the total population had adverse effects due to the infliximab.[27] In a retrospective study of 44 patients with refractory uveitis associated with Behcet's disease, notable reduction in the frequency of ocular inflammation was noted. However, frequent dosing was required to maintain the outcomes over a 5-year follow-up.[28] The common side effects of the treatment reported are headache, abdominal pain, rash, pneumonia, urinary tract infections, and reactivation of latent TB.[3]

Etanercept

Etanercept is a dimeric protein composed of TNF receptor2 and IgGFc fragment.[29] It inhibits both TNFα and TNFβ, thereby reducing formation of proinflammatory cytokines. Use of etanercept in ocular inflammation debatable, as it can worsen uveitis course or even induce inflammation as a paradoxical effect.[30-33] Foster *et al.* have compared the efficacy of etanercept with placebo, which showed failure to reduce the relapses in non-infectious uveitis case.[34]

Golimumab

Like adalimumab, golimumab is also a fully humanized monoclonal antibody. Hence the risk of allergic reactions and loss of efficacy are very less.[10] In a case of Bechet 's disease who was refractory to TNF-α blocker, reduction in inflammation and sustained remission was noted with the use of golimumab.[36] Authors have reported effective control of inflammation in refractory juvenile idiopathic arthritis-associated uveitis.[37] In a multicenter study of patients with ankylosing spondylitis-associated uveitis, reduction in the rate of uveitis recurrence and disease activity was noted with golimumab.[38]

Cetrolizumab

Cetrolizumab is a PEGylated humanized monoclonal antibody.[39] There are limited studies on the efficacy of cetrolizumab in uveitis. Favorable results have been noted in rheumatoid arthritis, spondyloarthropathies, and Crohn's disease.[39-41]

2. Anti-interleukin therapies

Interleukin IL-1β is a pro-inflammatory cytokine produced by the wide range of cells. Authors have found the role of IL-1β, IL-2, and IL-6 in autoinflammatory and autoimmune conditions.[42,43] Increased levels of interleukin are noted in aqueous humour, correlating with the disease severity.[44] Anti-interleukins drugs act against preventing the production of additional cytokines and pro-inflammatory molecules.

Anakinra

Binding of anakinra with ligands, a pro-inflammatory cytokine, prevents the mediated inflammation. In a study

Table 1: various types of biologics, their specific targets, route of administration, dosage, and side effects

Generic names	Specific targets	Route	Dosage	Description
TNF- inhibitors				
Adalimumab	TNF- α	SC Intravitreal	Initial dosage of 80 mg followed by 40 mg in subsequent weeks 0.03 mL (1.5 mg) at baseline, 2 weeks and once at a month for subsequent seven months	Allergic reactions, headache, malignancy, thrombolytic events, congestive heart failure, reactivation of TB
Infliximab	TNF- α	IV Intravitreal	3-5 mg at baseline,2nd and 6th weeks and every 4-8 weeks 1 mg/0.05 ml 6 weeks apart	Headache, abdominal pain, rash, pneumonia, urinary tract infection, reactivation of TB
Etanercept	TNF α and TNF β	SC	0.4 mg/kg twice a week	Rashes, diarrhea, infection
Golimumab	TNF- α	SC	50 mg per month	ANA positivity, development of infections
Certolizumab	TNF- α	SC	400 mg every week	Nausea, infections
Anti-interleukin therapy				
Anakinra	IL receptor	SC	100 mg/day	Headache, vomiting Antibody development, allergic reactions, fever, nasopharyngitis
Abatacept	T cells (CTLA-4)	IV	0.5-1g at loading, 1.25g SQ weekly in RA 0.1g to max of 1 g IV at baseline, 2nd and 6th	Headache, nausea, Nasopharyngitis, infections
Rituximab	B cells (CD20)	IV Intravitreal	375 mg/m^2 at 4 week intervals or 1,000 g/infusion 2 weeks apart. third dose interval is variable according to the disease severity 1mg/0.1ml monthly	Cardiovascular, fatigue, pruritis, nausea, urinary tract infections, antibody development, pulmonary disease
Interferons	No specific target	SC	3-6 million units daily with slow taper	Headache, fever, flu- like syndrome, hematological toxicity, elevated liver enzymes, depression, infections, fever, malignancy, arthritis, and thrombocytopenia
Fusion protein of CTLA-4				
Canakinumab	IL-1 β	IV, SC	150 mg for 6 weeks	Headache, vertigo, obesity, diarrhoea, musculoskeletal pain, skin reactions, nasopharyngitis
Gevokizumab	IL-1 β	IV, SC	60 mg every	Infections, hypersensitivity
Tocilizumab	IL-6R	IV	Initially 4 mg /kg once at every 4 weeks	Increased serum cholesterol, alanine, aminotransferase levels, injection site reaction
Secukinumab	IL-17A	IV	300 mg/kg	Headache, infections, gastrointestinal complications, hypercholesterolemia
Ustekinumab	Anti-IL-12 and IL-23	SC	45 mg at weeks 0 and 4 and every 12 weeks	ANA positivity, infections, nasopharyngitis
Alemtuzumab	Anti-CD52	IV	30 mg, thrice a week for 12 months	Headache, skin rashes, nausea, urinary tract, lymphocytopenia, thyroid disease, infusion related reaction, fever, nasopharyngitis

of nine patients who were treated with anakinra, including those having Behcet's disease refractory to TNF- α inhibitors, eight patients showed a complete resolution without any adverse effects.[45] Successful outcome was seen in patients with rheumatoid arthritis, chronic infantile neurological cutaneous articular syndrome, and cryopyrin-associated periodic syndrome.[46,47] Adverse effects include pneumonia and cellulitis.[10]

Abatacept

Abatacept is a fusion protein composed of cytotoxic T-lymphocyte antigen 4 molecule to a fragment of human immunoglobulin.[6] It inhibits the activation T lymphocytes by blocking CD28 and CD80/CD86 receptors.[48] A multicenter study done in patients with JIA-related uveitis used abatacept as first-line or second-line therapy showing a comparable improvement. In another report a 6-year-old child with JIA-associated uveitis, the use of abatacept showed a clinical improvement.[49]

Rituximab

Rituzimab is a chimeric monoclonal antibody directed against the activation of B-cell production.[6] A patient with retinal vasculitis who was resistant to conventional therapy was treated with rituximab and disease remission lasting up to 24 months was noted.[50] In a single-blinded study of patients with retinal vasulitis resistant to cytotoxic drugs, patients were randomized to receive either two courses of rituximab at a dose of 1000 mg twice a month along with oral prednesolone (0.5 mg/kg/day) and methotrexate (15 mg/week) or combination of cyclophosphamide (1000 mg/month), azathioprine (2-3 mg/kg/day), and prednesolone (0.5 mg/kg/day). Patients in rituximab treatment arm showed a significant improvement when compared to the other treatment arm. However, there was no statistically significant improvement in retinal vasculitis in both the arms. The side effects developed during the study period were conjunctivitis, pneumonia, and herpes zoster infection.[51] Possible side effects are fever, rash, respiratory symptoms, and hypertension.[10]

3. Interferons

Interferons are a group of cytokines in which type 1 includes IFNα and IFNβ and type II includes IFN- γ.[6] The immunoregulatory and immunosuppressive effects were found to be beneficial in the treatment of uveitis.[52] IFNα-2A and IFN α-2B are the two types of human recombinant IFNs produced by *Escherichia coli* by recombinant deoxyribonucleic acid technology. Half-life of the molecule has been increased in pegylated IFNs allowing longer duration of activity[6,10] Hatemi *et al.* have shown complete / partial remission of active disease in 94% of Behcet's disease associated-uveitis patients who were treated with interferon.[53] Other than Behcet's disease, interferon was found to be helpful in the management of sympathetic ophthalmia, Vogt-Koyanagi-Harda syndrome, birdshot chorioretinopathy, and serpiginous choroiditis.[54,10] Butler *et al.* have reported the efficacy of interferon in refractory uveitic cystoid macular edema.[55] The side effects of interferons are headache, fever, flu-like syndrome, hematological toxicity, elevated liver enzymes, and depression (Fig. 1).[56]

4. Fusion protein of CTLA-4

It is a new alternative tool that should be attempted when the conventional immunosuppressives and anti-TNF- α agents are ineffective.[57-58] Authors have reported its effectiveness in the management of severe uveitic cases.[7, 57-65] Interleukin (IL)-1 has shown to be a key proinflammatory cytokine in many autoimmune diseases and its inhibition might have a promising future among other novel therapeutic opportunities.[58]

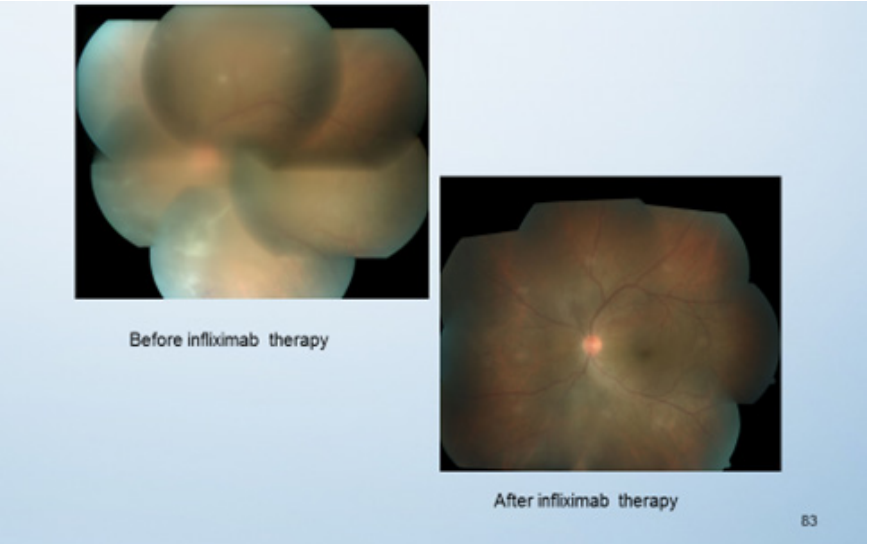
Canakinumab

Canakinumab is human monoclonal antibody acting against IL-1β.[57] In a report of 16-year-old female with a diagnosis of severe bilateral pan uveitis with retinal vasculitis refractory to other conventional therapies, a single subcutaneous injection of 150 mg canakinumab showed complete resolution of uveitis. The treatment effect lasted for 8 weeks.[58] A study to find the efficacy of canakinumab and anakinra in Bechet's disease concluded that canakinumab is successful in the management.[59] Canakinumab has been found to be effective in controlling recurrences and decreasing the chances of retinal vessel involvement in Bechet's disease.[60] Successful management has been reported in patients with JIA-related uveitis also.[61]

Gevokizumab

Gevokizumab is a monoclonal antibody that reduces the binding affinity of IL-1β. Gul *et al.* have investigated the safety, pharmacokinetics and clinical efficacy of gevokizumab in seven patients with acute posterior or panuveitis, and/or retinal vasculitis, resistant to azathioprine and/or ciclosporin, and receiving 10 mg/day or less of prednisolone. A single infusion of gevokizumab 0.3 mg/kg was administered in all patients. Rapid onset and sustained reduction in ocular inflammation was noted in four patients in median time of 14 days.[62] Acute ocular exacerbations were well controlled

Fig. 1: Fundus image of a patient with uveitis associated Bechet disease pre and post treatment



without the need for corticosteroids in patients with Behcet's disease-associated uveitis.[63] Adverse effects include infections and hypersensitivity reactions.[64]

Tocilizumab

Tocilizumab (myeloma receptor) is a recombinant IgG, which binds with IL-6 receptors and limits the expression of cytokines. In a retrospective study, tocilizumab effectively reduced the central foveal thickness in refractory CME. However, relapses were observed within 3 months after discontinuation of treatment.[65] Tocilizumab was useful in the management of JIA-related arthritis.[66] In a prospective study that included 25 patients of JIA, reduction in ocular inflammation was noted in 88.2% of cases with the use of tocilizumab.[67] Tocilizumab was successful in the treatment of rheumatoid arthritis. The common side effects include infections and hypersensitivity.[7]

Secukinumab

Secukinumab is a fully humanized monoclonal antibody targeting IL-17A. Increased level of IL-17 A has been found in the serum of patients with uveitis and immune-mediated systemic conditions like Vogt-Koyanagi-Harada syndrome and Behcet's disease.[68,69] A randomized trial study was conducted to explore the efficacy and safety of secukinumab at different dosage versus placebo in the management of non-infectious uveitis. Interim data analysis showed no significant difference between the groups in terms of recurrences.[70] Secukinumab has been proven to be effective in the treatment of anterior and posterior uveitis patients.[71]

Ustekinumab

Ustekinumab is a monoclonal antibody that specifically binds with the IL-12 and IL23 cytokines. It was found to be effective in alleviating inflammation in Crohn's disease.[72] In a patient with Behcet's disease, uveitis was successfully treated with ustekinumab.[73]

Alemtuzumab

Alemtuzumab acts against the cell surface CD52. Its effectiveness in various systemic autoinflammatory conditions (lymphocytic leukemia, multiple sclerosis, and rheumatoid arthritis) has been proven by many studies.[74] An indirect data analysis has reported the use of alemtuzumab in Behcet's-related uveitis. Out of four patients, complete remission was seen in 2 patients and partial remission in 2 patients after 6 months of treatment.[75]

Intravitreal injections of biologic agents in uveitis

Many studies have proven that intravitreal administration of drugs in uveitis is effective in reducing systemic side effects and improved inflammatory control.[76] Infliximab is a biological agent commonly used to treat many systemic autoimmune disease such as rheumatoid arthritis, inflammatory bowel disease, spondyloarthropathy and psoriasis.[3,6,10] The side effects of infliximab are well established.[3] A prospective, noncomparative, pilot study evaluated the effect of single intravitreal injection of infliximab (1 mg/0.05 ml) in 15 eyes with sight threatening relapsing uveitis in Behçet's disease. A significant improvement in BCVA by day 7 was noted, which maintained during the follow up period of 30 days.

However, persistent CME was noted in 80% of the eyes. No ocular or systemic side effects were documented during the study[77] Intravitreal infliximab of 1 mg/0.05ml was found to be rapid and safe, which can be used in cases contradicted to systemic route of administration.[77,78] Hamam *et al.* have conducted a nonrandomized prospective open labelled study to evaluate the short-term efficacy of intravitreal adalimumab (IVA) in active non-infectious uveitis. They reported injection of adalimumab 0.03 ml (1.5 mg) intravitreally at baseline, reinjection in an interval of 2 weeks and once at a month for subsequent 7 months was effective in controlling the inflammation, and decreasing the macular edema, Improvement in the best corrected visual acuity was noted in the majority of the cases.[79]

Points to remember while prescribing biologics

1. A complete systemic evaluation by a general physician is important to rule out any congestive heart failure, demyelinating diseases, malignancies, and infections.
2. Laboratory investigations:

Hematological analysis should be done before initiation of biologics and at the interval of 3 months while patients are on biologics.

- Liver and renal function tests including serum electrolytes, and glucose should be performed before starting therapy, and every 3-6 months while on treatment.
- TB skin test, QuantiFERON-TB gold or chest X-ray should be done annually in patients receiving biologic therapy
- HIV and hepatitis B and C before starting the therapy

3. Patients on anti-TNF therapy should be prepared to receive pneumococcal, influenza, and hepatitis B vaccines. It is contradicted to have live virus vaccines in patients started with anti-TNF therapy.

Conclusion

Biologics have emerged as a new weapon in the armamentarium of managing uveitis. However, there is limited literature evidence to corroborate the study findings on various drugs . The drugs are relatively costly and a complete work-up is needed before starting a biologic therapy.

Competing interests

The authors declare that they have no competing interests.

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