

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

The biological response modifiers are a new class of drugs which designed to block the activity of biologically active molecules. These drugs belong to several different classes depending on their action such as antitumor necrosis factor (TNF) agents, anti-interleukin (IL)-1 blockage, anti-IL6, anti-IL 17,  $\beta$ -cell blockers, and costimulatory blockade such as Abatacept. These are specific targeted therapies with concomitant decreased side effects but come with certain risks such as unmasking of latent tuberculosis with anti-TNF agents and lack of vaccine response for 6–12 months with B cell blockade.

Infliximab and Adalimumab are the two most commonly used biologics for noninfectious uveitis (NIU).<sup>[1]</sup>

### Infliximab

Infliximab is a chimeric monoclonal antibody against TNF- $\alpha$  with both human and murine components. Infliximab is currently FDA-approved for the treatment of rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis.<sup>[1]</sup>

Infliximab can be used as first-line therapy for selected systemic diseases such as Adamantiades-Behçet's disease or in cases of moderate-to-severe idiopathic retinal vasculitis and optic disc inflammation, or as third-line therapy in uveitis refractory to corticosteroids and conventional immunomodulatory agents.<sup>[1]</sup>

Infliximab is given intravenously at doses of 5, 7.5, 10, or 20 mg/kg<sup>[2,3]</sup> every 4 to 8 weeks with or without concomitant intravenous methylprednisolone at doses of 500 to 1000 mg for 1 to 3 days monthly. Doses can be tapered and intervals are extended based on the clinical response. The mean number of

infusions to show initial effectiveness is 2.05 and mean number of infusions to achieve quiescence is 9.17 among patients with Vogt-Koyanagi-Harada (VKH), sarcoidosis, juvenile idiopathic arthritis (JIA), and idiopathic uveitis.<sup>[2]</sup> Initial anecdotal evidence suggests that the standard dose of infliximab (less than 10 mg/kg/dose) is less effective in the treatment of chronic uveitis.<sup>[2,3]</sup>

The half-life of infliximab is 10 days; however, its effects may persist for up to 2 months.<sup>[4]</sup> Because of its chimeric nature, infliximab is recommended to be administered concurrently with methotrexate or other immunomodulatory agents to decrease antichimeric antibody formation and increase the duration of drug efficacy.

### Adalimumab

Adalimumab is a fully humanized monoclonal antibody against TNF- $\alpha$ , which binds soluble and transmembrane TNF- $\alpha$ . The United States Food and Drug Administration (FDA) approved adalimumab for the treatment of NIU after two successful phase-3 multicenter randomized controlled clinical trials, VISUAL I and II, demonstrated that time to treatment failure was significantly longer in the adalimumab group (>18 months) compared to the placebo group (8.3 months).<sup>[5]</sup>

Currently, adalimumab may be considered as first-line therapy for JIA-associated anterior uveitis or Behçet's disease-related panuveitis. Additional studies have supported the use of adalimumab in patients with Behçet's disease-related panuveitis, sarcoidosis-related uveitis, VKH syndrome, and birdshot chorioretinopathy.<sup>[6]</sup>

Adalimumab is given subcutaneously with a loading dose of 80 mg followed by biweekly doses of 40 mg in adults and 20 to 40 mg in children, depending on body weight, every other week. Patients weighing  $\geq 40$  kg received 20 to 40 mg every other week, whereas patients weighing  $\leq 40$  kg received 10 to 20 mg every other week. The doses can escalate to weekly if needed or be extended to every 3 weeks. Such frequency was chosen due to a half-life of 15–19 days.<sup>[7]</sup> The rapid onset of response for uveitis was found after 2 to 16 weeks (mean 6 weeks) and was effective in 83% of children with severe JIA-associated uveitis. Adalimumab can be used as monotherapy or in combination

with systemic steroids or disease-modifying antirheumatic drugs, such as mycophenolate mofetil, azathioprine, methotrexate, or cyclosporin A.

TNF- $\alpha$  inhibitors like infliximab are contraindicated in multiple sclerosis. Infections such as tuberculosis (TB), human immunodeficiency virus, syphilis, hepatitis B virus, hepatitis C virus, and toxoplasma must be ruled out before initiating therapy. Common side effects of TNF- $\alpha$  inhibitors include hypersensitivity, while more severe side effects include serious infections, hematologic reactions, malignancies, and myocardial infarctions.

Patients on TNF- $\alpha$  inhibitors require regular blood evaluations including complete blood count, liver function tests, blood urea nitrogen, and serum creatinine levels every 6 to 12 weeks.

Apart from infliximab and adalimumab, there are now other agents also which are emerging as options in the treatment of noninfectious uveitis including tocilizumab, sarilumab, and sirolimus which have shown encouraging outcomes in the treatment of NIU with regard to minimizing corticosteroid dosage, reducing vitreous haze score ( $\geq 2$  steps), and improving visual acuity with a relatively benign safety profile. Other promising therapies, including certolizumab, canakinumab, anakinra, IFN- $\alpha$ , abatacept, and adrenocorticotrophic hormone have demonstrated efficacy in small case reports.

Thus, biologicals can be a useful alternative for the management of noninfectious uveitis and also in cases of recalcitrant conventional immunosuppression.<sup>[8]</sup> However, a limitation in current times can be their cost and caution needs to be exercised in a TB endemic country like India.

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