Tofacitinib in recalcitrant scleritis: First case report from India

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A 65-year-old male presented with redness and pain associated with active necrotizing scleritis in the left eye. He was started on mycophenolate mofetil and oral corticosteroids, to which there was no response detected after 4 weeks. A rheumatology opinion was sought and he was started on tofacitinib, after which there was dramatic clinical improvement. Patients refractory to conventional immunosuppressive therapy can benefit from the new class of immunosuppressive agents, JAK/STAT kinase inhibitors.

Key words: Immunosuppressive treatment, JAK/STAT inhibitors, necrotizing scleritis, tofacitinb

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_534_20

Scleritis is a potentially blinding disease involving chronic inflammation of the sclera. About 50% of scleritis cases are associated with systemic conditions.[1] The management of scleritis is challenging and often requires a multidisciplinary approach. Because of its chronic course and recurrent and severe nature of the inflammation, various immunomodulatory agents, ranging from corticosteroid to biologics, has been tried in the management of scleritis. In recent years, many new drugs have have added to our armamentarium against scleritis. Among these, there is a new class of immunomodulatory agents,

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Received: 13-Mar-2020 Revision: 22-Apr-2020
Accepted: 13-May-2020 Published: 20-Aug-2020

Cite this article as: Pyare R, Kaushik V, Dutta Majumder P, Biswas J. Tofacitinib in recalcitrant scleritis: First case report from India. Indian J Ophthalmol 2020;68:1988-90.

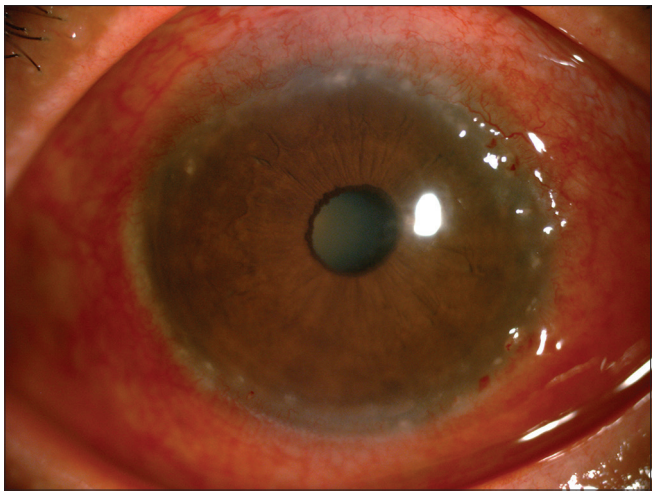

Figure 1: Pretreatment picture showing deep episcleral congestion, active necrotizing scleritis with immature senile cataract

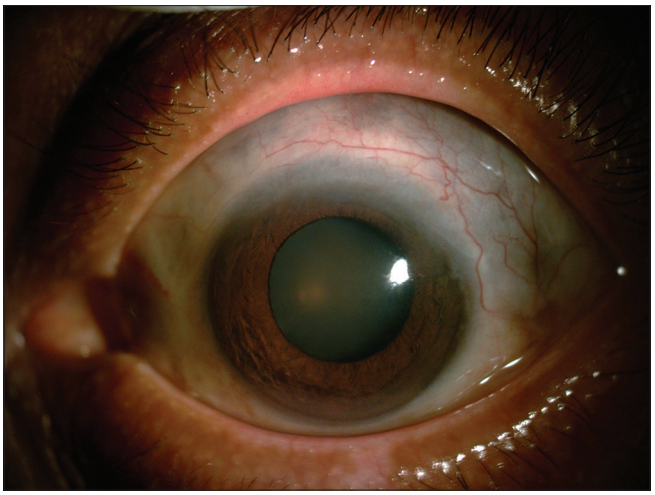

Figure 2: Posttreatment with tofacitinb (1 month) showing completely resolved scleral inflammation

the *Janus Kinase* Inhibitors (JAK/STAT pathway inhibitors) which include baricitinib, tofacitinib and upadacitinib. Tofacitinib has been approved by the Food and Drug Administration, USA for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis. Few isolated case reports have described their use in refractory uveitis. A Medline search showed that this drug has never been used in India for the treatment of refractory scleritis. We report a case of refractory scleritis which responded to tofacitinib therapy.

Case Report

A 65-year-old hypertensive but otherwise healthy Indian male presented to our clinic with complaints of redness and severe pain with diminution of vision for the last 2 years in the left eye. He had earlier consulted elsewhere and been diagnosed with scleritis and treated with oral steroids and oral non-steroidal anti-inflammatory drugs (NSAIDs) along with topical steroids on and off for 2 years. On presentation, he had a best corrected visual acuity (BCVA) of 6 / 6 in the right eye and 6 / 36 in the left eye. At the time of presentation to us, he had stopped all medications. Anterior segment examination of the left eye showed deep episcleral congestion, thinning of sclera superiorly, active necrotizing scleritis with anterior chamber reaction of cells 1+ and flare 1+ with immature senile cataract [Fig. 1]. The blood investigations for Rheumatoid factor, antinuclear antibody, Antineutrophilic cytoplasmic antibody, Anti-citrullinated protein antibody, HLA B 27, *Treponema Pallidum* haemagglutination test were all negative. The patient was started on prednisolone tablet 1 mg/kg per day and mycophenolate mofetil tablet 1000 mg twice a day. On review, after one month, the patient did not show any improvement. At this point, in consultation with a rheumatologist, the patient was started on tofacitinib tablet (5 mg twice a day). On second review after another month, the patient reported remarkable improvement in symptoms, despite BCVA remaining 6 / 24 probably due to increasing cataract. On examination, the scleral inflammation had completely resolved, the anterior chamber reaction had subsided and the cornea was clear [Fig. 2]. The patient was kept under close follow-up, with subsequent slow tapering of tofacitinib. On the last follow-up, the patient was stable on tofacitinib 5 mg on alternate day, mycophenolate mofetil 500 mg twice a day and prednisolone tablet 2.5 mg on alternate day.

Discussion

Tofacitinib is a small molecule that reversibly inhibits Janus Associated Kinases, particularly JAK1 and JAK3. Janus Associated Kinases are intracellular cytoplasmic tyrosine kinases. They are involved in transferring cytokine mediated signals via Signal Transducers and Activators of Transcription (STAT) to cellular DNA. Many cytokines are implicated in the pathophysiology of uveitis, many of which are blocked by JAK/STAT inhibitors, including IL 2, IL 4, IL 15, IL 21.[2,3] This leads us to believe JAK/STAT inhibitors would be effective in cases of uveitis. Besides, tofacitinib is also FDA approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative arthritis, all of which are frequent systemic associations of scleritis suggesting it may be efficacious in resolution of the uveitis component of the disease as well.

Paley *et al*. have described 2 cases of recalcitrant uveitis and scleritis which responded to tofacitinib after failure or intolerance to multiple immunomodulatory regimes. They report time taken for effective clinical response to be 3-4 weeks, which is the same as the period taken for effective clinical response in our patient.[4] Bauermann *et al*. reported the successful treatment of a case of JIA (juvenile idiopathic arthritis) associated recalcitrant cystoid macular edema being effectively treated with tofacitinib.[5] Miserocchi *et al*. have described a case series of 4 patients with JIA with severe, recalcitrant associated uveitis in which baricitinib and tofacitinib were used to control systemic and ocular inflammation. Baricitinib and tofacitinib were used to control systemic and ocular inflammation.[6] Besides uveitis, there have been reports of use of topical use of tofacitinib 0.003% for treatment of dry eye, with evidence showing reduced expression of inflammatory mediators in the cornea.[7-9]

Medline search revealed that this is the first report of use of JAK/STAT inhibitors in necrotizing scleritis from India. In our case, the patient presented with active, severe inflammation despite being on treatment for 2 years. The severity of the inflammation, along with the vision threatening nature of

the disease prompted us to try tofacitinib in this patient. The patient had failed to respond to oral corticosteroids, and to oral steroids in conjunction with mycophenolate mofetil. There was a dramatic clinical improvement after tofacitinib was added to this combination. The treatment was well tolerated with no adverse effects.

Conclusion

Our case showed that the uveitis and necrotizing scleritis patients who are refractory to treatment with oral corticosteroids and immunomodulatory drugs can benefit from this new class of JAK inhibitors. There has been increasing scientific interest on this topic, with case reports showing good efficacy and safety profile for tofacitinib, but further studies are required to confirm these data.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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