



Case report

Tofacitinib for refractory uveitis and scleritis

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ARTICLE INFO

Keywords:

Uveitis
Scleritis
Tofacitinib
JAK
STAT

ABSTRACT

Purpose: To report the successful use of tofacitinib in the treatment of refractory uveitis and scleritis.

Observations: Two patients, one with scleritis and another with anterior and intermediate uveitis, presented with refractory disease after failure of multiple steroid-sparing therapies. Treatment with tofacitinib led to durable resolution of uveitis and scleritis.

Conclusions and importance: Tofacitinib is a potential novel treatment option for refractory, noninfectious inflammatory eye disease.

1. Introduction

Noninfectious uveitis and scleritis can occur in isolation or in the context of a systemic inflammatory condition. Uncontrolled ocular inflammation can lead to a number of vision-threatening ocular complications, including cataract formation, glaucoma, cyclitic membrane formation, retinal edema, hypotony, perforation, and even blindness.^{1,2} Although corticosteroids (topical drops, local injections and systemic) are effective therapies for ocular inflammatory disease, the ocular and systemic side effects of corticosteroids often preclude long-term use. Adalimumab (AbbVie, North Chicago, IL) is the only steroid-sparing agent currently FDA-approved for the treatment of uveitis, however, it is effective only in a subset of patients.^{3,4} Thus, other effective steroid-sparing therapies are needed for the treatment of noninfectious inflammatory eye disease.

Tofacitinib (Pfizer, Inc., New York City, NY) is an oral medication for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis.^{5–8} It is a small molecule that reversibly inhibits Janus associated kinases (JAKs) with some selectivity for JAK1 and JAK3.⁹ JAKs execute cytokine receptor signaling by phosphorylation and activation of signal transducers and activator of transcription (STAT) proteins, which subsequently dimerize, enter the cell nucleus, and initiate transcription of numerous inflammatory genes. Several inflammatory cytokines that have been implicated in pathogenesis of ocular inflammation are

known to utilize the JAK/STAT signaling pathway, including interleukin-2 (IL-2) and IL-6.^{10–12} However, there have not been reports that treatment with tofacitinib ameliorates ocular inflammation. Here, we describe the effective use of tofacitinib in combination with methotrexate for the treatment of noninfectious uveitis and scleritis in two patients whose disease was refractory to methotrexate monotherapy and to other steroid-sparing therapies.

1.1. Findings

Case 1. A 45-year-old woman with a past medical history of migraines, anemia, and major depressive disorder presented with a several-month history of eye pain, photophobia and headache, associated with diarrhea and inflammatory back and peripheral joint pain. She was diagnosed with bilateral anterior uveitis with hypopyon. Laboratory studies were negative for an infectious etiology but positive for an HLA-B27 allele. However, objective evidence of an underlying systemic disease with x-rays, MRI, and colonoscopy did not support a definitive diagnosis of systemic disease.

Her uveitis was refractory to topical steroids and local steroid injections with anterior chamber cell fluctuating between 2 + cell and hypopyon. Oral steroids (prednisone 80 mg twice daily) improved the uveitis to 0.5 + cell in both eyes but were not tolerated due to worsening anxiety. She subsequently developed vitritis and cystoid macular

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<https://doi.org/10.1016/j.ajoc.2018.12.001>

Received 8 August 2018; Received in revised form 12 October 2018; Accepted 3 December 2018

Available online 04 December 2018

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edema (CME).

Monotherapy with methotrexate, leflunomide, azathioprine, and mycophenolate were all ineffective. Although anti-TNF agents (adalimumab; infliximab, Janssen Biotech, Inc., Horsham, PA; certolizumab pegol, UCB, Brussels, Belgium) effectively controlled her ocular inflammation, these treatments were not tolerated due to injection site reactions, infusion reactions, and recurrent infections, which led to discontinuation of biologic therapy. She underwent bilateral implantation of fluocinolone acetonide intravitreal implants (Baush and Lomb, Rochester, NY) for vitritis and CME, and her uveitis improved initially. However, she had recurrence of cell in her left eye and cystoid macular edema in her right eye within 12 months of implantation.

She was initiated on tofacitinib extended-release 11 mg daily with concurrent methotrexate therapy without topical steroids. After 4 weeks of combination therapy, her systemic symptoms and uveitis resolved with no visible cell. The patient subsequently discontinued methotrexate but continued tofacitinib. Although her systemic complaints of joint pain, morning stiffness, diarrhea, and abdominal pain worsened, her uveitis remained controlled with no cell in the left eye and 0.5 + cells in the right eye after 3 months of tofacitinib therapy.

Case 2. A 40-year-old woman with a past medical history of hypothyroidism and type II diabetes mellitus presented with ocular pain, redness, swelling and light sensitivity involving both eyes. She was seen by a local ophthalmologist and diagnosed with scleritis. Her ocular inflammation was refractory to topical steroid drops, and a local steroid injection led to only transient relief. Oral prednisone was effective, but she was unable to taper below 12 mg of prednisone daily without a flare of her disease.

A rheumatologic evaluation did not identify an underlying systemic infectious or inflammatory disease. Steroid-sparing therapy with methotrexate and mycophenolate were both ineffective as monotherapy. Although two courses of azathioprine led to moderate improvement in her scleritis, she could not tolerate it due to recurrent cutaneous and enteric ulcers. Oral cyclophosphamide induced disease remission, but was complicated by extreme fatigue and hematuria, leading to its discontinuation.

Tofacitinib extended-release 11 mg daily was prescribed. Two weeks after cessation of cyclophosphamide and initiation of tofacitinib, the patient presented with a recurrence of her scleritis. Methotrexate was added to tofacitinib, and her scleritis resolved with one week. The timing of disease remission suggested tofacitinib was the effective agent as the therapeutic response to methotrexate had previously failed as monotherapy in this patient, and also because methotrexate typically requires approximately 6 weeks for a clinical response. Over the subsequent 9 months, combination therapy with tofacitinib and methotrexate has maintained disease remission in this patient.

2. Discussion

Monoclonal antibodies that block IL-2, IL-6, and IL-23, which all activate JAK-STAT signaling, have been reported to be efficacious in uveitis.^{13–16} This implies that targeting JAK-STAT signaling may be effective in uveitis, but this is the first report of a favorable clinical response of ocular inflammation to tofacitinib. In addition, tofacitinib proved to be effective for a patient with refractory scleritis that was only initially controlled with cyclophosphamide.

In both cases, clinical efficacy of tofacitinib was noted approximately four weeks after the initiation of therapy. This rate of improvement parallels prior trials in rheumatoid arthritis and psoriatic arthritis.^{5,7} Additionally, both patients achieved low disease activity with combination therapy of tofacitinib and methotrexate, which has higher rates of efficacy than tofacitinib monotherapy in the setting of rheumatoid arthritis.¹⁷ Tofacitinib monotherapy was sufficient to maintain low disease activity in the patient with uveitis. Whether monotherapy with tofacitinib would have controlled disease in the

patient with scleritis cannot be stated definitively, although this seems likely given the fact that remission was induced without corticosteroids, and just one week after adding methotrexate to tofacitinib.

Although adalimumab can provide a durable clinical response, it is only effective in 40–60% of uveitis cases.^{3,4} In addition, biologic DMARDs (disease-modifying antirheumatic drugs) can be associated with other adverse drug events (e.g., injection site reactions or infusion reactions) that may necessitate discontinuation of these agents. Furthermore, anti-drug antibodies against biologic therapy can limit long-term efficacy of monoclonal antibodies or soluble receptors.¹⁸

JAK inhibitors may have advantages over traditional biological DMARDs. Since tofacitinib is a small molecule, it may more efficiently cross the blood-aqueous or blood-retinal barrier. Whereas local injection of biologic agents can elicit inflammatory responses and contribute to retinal toxicity,^{19,20} topical administration of small molecules may control ocular inflammation with better tolerability. In support of this hypothesis, tofacitinib administered topically was effective in a mouse model of corneal inflammation.²¹ In further support of a role for tofacitinib in ocular disease, an 8-week administration of topical tofacitinib was well tolerated and reduced markers of ocular inflammation in the setting of dry eye disease.^{22,23}

Since tofacitinib inhibits multiple JAK family members, the relative importance of the different JAK family members (JAK1, JAK2, JAK3, and Tyk2) and their corresponding cytokine (e.g. IL-2, IL-6, IL-12, IL-23, and interferons) remains to be determined. The JAK inhibitors baricitinib (Eli Lilly and Company, Indianapolis, IN) and filgotinib (Gilead Sciences, Inc., Foster City, CA and Galapagos NV, Mechelen, Belgium) may also be effective for the treatment of non-infectious ocular inflammation. Baricitinib, which preferentially inhibits JAK1 and JAK2, is effective for the treatment of rheumatoid arthritis^{24,25} and has been recently reported to ameliorate ocular disease in a case of off-label use for mucous membrane pemphigoid.²⁶ In addition, a Phase II placebo-controlled trial of filgotinib, a preferential JAK1 inhibitor, is currently underway for the treatment of non-infectious uveitis (NCT03207815). Lastly, larger studies of different JAK inhibitors will be necessary to define the risk-benefit ratio of inhibitors that target distinct JAK family members.

Tofacitinib is FDA-approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis,^{5–8} which are systemic diseases associated with scleritis and uveitis. Phase 2 studies also suggest that tofacitinib may be efficacious in ankylosing spondylitis.²⁷ Although treatment of these systemic diseases with other agents may lead to the resolution of their ocular manifestations, the relative efficacy of tofacitinib for systemic disease-associated uveitis remains to be carefully defined. Our case series may provide impetus for further testing of tofacitinib for noninfectious uveitis and scleritis, both in the presence and absence of systemic rheumatologic disease.

3. Conclusions

Severe recurrent or chronic ocular inflammation can lead to vision-threatening complications. These patients require effective immunomodulating therapy that controls inflammation while minimizing corticosteroid-associated side effects and complications. Our cases suggest that tofacitinib is likely to be an effective steroid-sparing agent for noninfectious inflammatory eye disease, at least in a subset of patients.

Patient consent

The patients provided verbal consent to publication of these cases. IRB exemption was obtained for this publication.

Acknowledgments and disclosures

Funding

No funding or grant support.

Conflicts of interest

The following authors have no financial disclosures: M.A.P., H.K., P.K.R., T.P.M., and J.J.M.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Acknowledgments

This work was supported by NIH/NIAMS (USA) 5 T32 AR007279-39 (M.A.P.).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajoc.2018.12.001>.

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