Tofacitinib for refractory ocular mucous membrane pemphigoid

Hayley James [a], Grace L. Paley [a], Richard Brasington [a,b], Philip L. Custer [a], Todd P. Margolis [a], Michael A. Paley [b,*]

[a] Department of Ophthalmology and Visual Sciences, Washington University in Saint Louis, Center for Outpatient Health, 6th floor, 4901 Forest Park Avenue, Saint Louis, MO, 63110, USA
[b] Division of Rheumatology, Department of Medicine, Washington University in Saint Louis, Center for Advanced Medicine, 5th floor Suite C, 4921 Parkview Place, Saint Louis, MO, 63110, USA

ABSTRACT

Purpose: To report the successful use of tofacitinib in the treatment of refractory ocular mucous membrane pemphigoid (MMP).
Observations: Two patients with ocular MMP presented with refractory disease after failure of multiple therapies. Treatment with tofacitinib led to durable control of conjunctival inflammation within 8 weeks and no apparent progression of sub-conjunctival fibrosis. One patient maintained absence of apparent disease activity over 16 months of follow-up. Cessation of tofacitinib in the other patient led to disease relapse which was reversed by re-initiation of therapy.
Conclusions and importance: Small molecule inhibitors of Janus kinases, such as tofacitinib, may offer an effective treatment option for refractory ocular MMP.

1. Introduction

Mucous membrane pemphigoid (MMP) encompasses a heterogenous group of autoimmune subepithelial blistering disorders that affect skin and mucosal membranes. Affected tissues include oral, ocular, tracheal, esophageal, nasopharyngeal, anogenital, and genitourinary tissues.[1] Ocular involvement, formerly known as ocular cicatricial pemphigoid, occurs in approximately 70% of MMP cases. This presents as a chronic, progressive, cicatrizing conjunctivitis which can cause significant vision loss due to corneal limbal stem cell failure, corneal neovascularization, keratinization of the corneal surface, keratitis sicca and other forms of corneal opacification.[1–3] The conjunctival changes frequently result in secondary cicatricial entropion of the eyelids, which can further compromise the cornea. Topical therapy is insufficient to control the progression of conjunctival scarring.[4] Systemic corticosteroids, while effective for acute control of symptoms, have not been shown to be effective for adequate sustained immunosuppression and risk a myriad of adverse effects associated with long-term use.[5] Current therapeutic options for severe MMP include anti-proliferatives, such as methotrexate, azathioprine, mycophenolate mofetil, or cyclophosphamide, tumor necrosis factor (TNF) inhibitors, B cell depletion, and intravenous immunoglobulin (IVIg).[6] Unfortunately, medication-related adverse events or therapeutic inefficacy may necessitate additional treatment options.

Tofacitinib (Pfizer, Inc., New York City, NY) is an oral medication that is FDA-approved for the treatment of rheumatoid arthritis, ulcerative colitis, and psoriatic arthritis.[7–10] It is a reversible Janus kinase (JAK) inhibitor, preferentially acting on JAK1 and JAK3, and to a lesser extent, JAK2.[11] JAKs participate in the signaling pathways of multiple cytokines through phosphorylation and activation of signal transducers and activators of transcription (STAT) proteins.[11,12] The cytokines primarily include IL-2, -4, -7, -9, -15, and −21, but also interferon (IFN)-γ, IL-6, and to a lesser degree, IL-13.[11,12] Tofacitinib has additionally been shown to suppress TNF, IL-1β, and type I interferon production in monocyte-derived dendritic cells stimulated with antigenic lipopolysaccharide *in vitro*.[13]

The pathogenesis of MMP is thought to involve a type 2 hypersensitivity reaction with autoantibodies against multiple conjunctival basement membrane zone antigens, including the cytoplasmic domain of the β4 peptide of α6β4 integrin.[14,15] Additionally, affected stroma and conjunctiva contain elevated levels of IL-1, -6, -12, 13, and −17.[15] Thus, inhibition of JAK signaling has the potential to block multiple

---

inflammatory pathways thought to be involved in the pathogenesis of MMP.

A recent publication has reported the effective use of the preferential JAK1/JAK2 inhibitor baricitinib (Eli Lilly and Company, Indianapolis, IN) in a case of severe, refractory ocular MMP.[16] Notably, JAK inhibition was effective despite prior treatment failure with methotrexate, mycophenolate mofetil, IVIg, adalimumab (Abbvie, North Chicago, IL), rituximab (Genentech, South San Francisco, CA), and cyclophosphamide. However, whether this efficacy is restricted to baricitinib alone or is shared with other JAK inhibitors remains unclear. We recently had the opportunity to treat effectively two patients with refractory ocular mucous membrane pemphigoid with tofacitinib.

2. Findings

Case 1: A 79-year-old woman with a past medical history of hypertension and hyperlipidemia presented with a one-year history of worsening bilateral ocular discomfort, redness, and tearing. She denied long-term use of topical eye drops, ocular trauma, atopic disease, prior ocular infections, SJS/TEN or prior ocular surgery. She denied nasal, oral, and genital ulcers. On exam, she had bilateral lower eyelid cicatricial entropion with forniceal shortening, symblepharon, tarsal fibrosis, and corneal neovascularization (Fig. 1). She was diagnosed with ocular MMP. Given the advanced degree of cicatricial changes at presentation, topical therapy was passed over in favor of systemic treatments. Monotherapy with methotrexate, mycophenolate mofetil, and rituximab (1g

IV x 2 infusions separated by 14 days) was ineffective after 4-month courses each. Cyclophosphamide up to 1000 mg/m^2 IV was trialed after this, but did not achieve resolution of conjunctival inflammation after 5 monthly cycles of therapy. IVIg subsequently led to a partial, but incomplete, response after 2 months of therapy.

We added tofacitinib 11 mg extended-release daily by mouth to her therapeutic regimen of IVIg every 3 weeks. After 8 weeks, she had marked improvement in her ocular inflammation. Although she had already developed forniceal shortening, symblepharon, and subconjunctival fibrosis, she had near-resolution of her conjunctival injection and active inflammation. She achieved essentially quiet disease, with trace superior tarsal injection, after 8 months of combination therapy that was sustained for 4 more months (Fig. 1). The patient subsequently discontinued IVIg due to cost but remained free of further conjunctival inflammation on tofacitinib monotherapy for an additional 12 months, up to the time of this submission. She did not experience any adverse drug events or laboratory abnormalities during this follow-up period.

Case 2: A 70-year-old man with a past medical history of type 2 diabetes mellitus and myocardial infarction with subsequent stenting presented with one year of right eye irritation and tearing. He also noted a recent history of oral ulcers and difficulty swallowing. He had used topical erythromycin ophthalmic ointment and cyclosporine ophthalmic emulsion, 0.05% (Allergan, Dublin, Ireland) for the 4 months preceding his presentation without improvement, but no other topical medications. On exam, he had significant symblepharon of the lower eyelids bilaterally with forniceal shortening and cicatricial entropion of the

Fig. 1. Color photographs of case 1 before and after treatment with tofacitinib.

right lower eyelid with trichiasis. He was diagnosed with probable ocular MMP but was lost to follow-up.

One year later, he returned to clinic with active disease. Biopsies of his oral and nasal ulcers were consistent with MMP. Treatment with methotrexate monotherapy and mycophenolate mofetil monotherapy was ineffective. His ocular inflammation improved on combination therapy with mycophenolate mofetil and low-dose oral cyclophosphamide, although his oral ulcers persisted. Due to cost and concern for bladder toxicity with cyclophosphamide, he was switched to rituximab in combination with mycophenolate mofetil with relapse of disease activity after 18 months.

Rituximab was discontinued and replaced with tofacitinib 11 mg extended-release daily by mouth with concurrent mycophenolate mofetil 1g twice daily by mouth. After 8 weeks of tofacitinib, his ocular inflammation had resolved, as did his nasal and oral ulcers. These changes persisted at 6 months. Unfortunately, due to cost, he was off tofacitinib for over a month with return of conjunctival injection and active inflammation. This resolved after restarting tofacitinib, with quiet disease again 4 months later on follow-up. His nasal and oral ulcers did not recur during this time period. In addition, he did not experience any adverse drug events or laboratory abnormalities during the follow-up period.

3. Discussion

Cyclophosphamide has demonstrated robust clinical efficacy in patients with MMP[17]; however, the risks associated with long-term use, such as hemorrhagic cystitis, bladder cancer, and bone marrow suppression, can limit enthusiasm for this potent therapy. Fortunately, additional therapies have become available for the treatment of MMP, such as B cell depletion with rituximab.[6] Indeed, interest in this strategy has led to the initiation of a clinical trial comparing the efficacy of cyclophosphamide and rituximab (NCT03295383). As our cases highlight, however, not all patients are responsive to B cell depletion. Thus, to effectively control MMP, clinicians may need multiple options in their armamentarium, one of which may be JAK inhibitors.

While a previous group has reported clinical efficacy of the preferential JAK1/JAK2 inhibitor baricitinib in ocular MMP,[16] it has not been known whether this would hold true for other JAK inhibitors. The two patients in this report demonstrate that the preferential JAK1/JAK3 inhibitor tofacitinib can also be an effective therapy for ocular MMP. Based on these reports, it would be reasonable to hypothesize that JAK1 inhibition is a key shared feature that could be responsible for the therapeutic efficacy of both baricitinib and tofacitinib. JAK inhibitor selectivity, however, is determined based on *in vitro* assays, and their preferential inhibition *in vivo* in human patients is still not well understood.[18] Indeed, JAK inhibitors are quite promiscuous in the number of signaling pathways affected.[18] While this treatment strategy may seem less targeted compared to cytokine blockade with monoclonal antibodies, it may be advantageous to clinicians who do not yet have the tools to identify relevant pathogenic processes in a rare and poorly understood disease such as MMP.

As with many autoimmune conditions, there are no current laboratory tests or biomarkers that are able to predict response to therapy in MMP. While some patients are responsive to the initial medication selected, others undergo multiple courses of different therapies until they demonstrate a clinical improvement. Therefore, JAK inhibitors, which have a rapid clinical onset of 1–4 weeks,[10,19–21] may be particularly advantageous. Accordingly, both patients in this report demonstrated a clinical response after 8 weeks of tofacitinib. This rate of clinical response was similar to the previous report using baricitinib in MMP.[16] Thus, JAK inhibitors may offer a valuable option for select patients with severe ocular MMP, particularly in individuals who have already experienced significant fibrosis and require rapid control of active disease.

In both patients in this report, tofacitinib treatment led to disease control in the setting of combination therapy, with either IVIg or mycophenolate mofetil. While combination therapy introduces challenges in determining the relative contributions of each therapy, there is clinical evidence in each case that suggests that tofacitinib played a key role in limiting conjunctival inflammation. In the first case, the patient discontinued combination therapy with IVIg and was able to maintain clinical quiescence on tofacitinib monotherapy. In the second case, the patient experienced a disease flare after cessation of tofacitinib therapy and quiet disease was achieved again after reinitiating tofacitinib. As a result, it appears likely that, in both cases, tofacitinib was critical in controlling conjunctival inflammation. Whether JAK inhibitors are able to induce clinical remission in MMP as monotherapy remains an open question. However, this seems possible given the fact that tofacitinib has robust effectiveness as monotherapy in multiple other autoimmune conditions.[8–10] Unfortunately, clinicians may have difficulty obtaining coverage for these medications, as JAK inhibitors are currently not FDA-approved for the treatment of MMP.

As a class, JAK inhibitors show promise for ocular inflammatory disease. For example, clinicians have reported efficacy for both tofacitinib and baricitinib in cases of refractory scleritis and uveitis.[22–24] In addition, interventional trials testing the efficacy of tofacitinib (NCT03580343), baricitinib (NCT04088409), and filgotinib (Gilead, Foster City, CA) (NCT03207815) in non-infectious uveitis are now underway. As JAK inhibitors have demonstrated superiority to *anti*-TNF monoclonal antibodies in rheumatoid arthritis,[19,20] the results of these clinical trials should prove instructive, especially in studies that directly compare the two drug classes (NCT04088409).

4. Conclusions

Mucous membrane pemphigoid produces relapsing, progressive cicatricial conjunctivitis and ocular inflammation, which often leads to significant vision loss. These patients require effective systemic immunomodulatory therapy to control their ocular inflammation and preserve vision. The two cases described here suggest that JAK inhibitors, such as tofacitinib, could be a viable option for mucous membrane pemphigoid, at least in some patients, and would benefit from further study.

Patient consent

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

Authorship

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

Declaration of competing interest

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

R.B. receives speaking fees from Pfizer. P.L.C. owns stocks in Pfizer.

research.

References

1. Ong HS, Setterfield JF, Minassian DC, Dart JK, Mucous Membrane Pemphigoid Study G. Mucous membrane pemphigoid with ocular involvement: the clinical phenotype and its relationship to direct immunofluorescence findings. *Ophthalmology*. 2018;125:496–504.
2. Saw VP, Dart JK, Rauz S, et al. Immunosuppressive therapy for ocular mucous membrane pemphigoid strategies and outcomes. *Ophthalmology*. 2008;115:253–261 e1.
3. Georgoudis P, Sabatino F, Szentmary N, et al. Ocular mucous membrane pemphigoid: current state of pathophysiology, diagnostics and treatment. *Ophthalmol Ther*. 2019;8:5–17.
4. Foster CS. Cicatricial pemphigoid. *Trans Am Ophthalmol Soc*. 1986;84:527–663.
5. Sharon Y, Chu DS. Adrenocorticotropic hormone analogue as novel treatment regimen in ocular cicatricial pemphigoid. *Am J Ophthalmol Case Rep*. 2018;10: 264–267.
6. Buonavoglia A, Leone P, Dammacco R, et al. Pemphigus and mucous membrane pemphigoid: an update from diagnosis to therapy. *Autoimmun Rev*. 2019;18: 349–358.
7. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012;367:508–519.
8. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367:495–507.
9. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376:1723–1736.
10. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med*. 2017;377:1537–1550.
11. Flanagan ME, Blumenkopf TA, Brissette WH, et al. Discovery of CP-690,550: a potent and selective Janus kinase (JAK) inhibitor for the treatment of autoimmune diseases and organ transplant rejection. *J Med Chem*. 2010;53:8468–8484.
12. Seif F, Khoshmirsafa M, Aazami H, Mohsenzadegan M, Sedighi G, Bahar M. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. *Cell Commun Signal*. 2017;15:23.
13. Kubo S, Yamaoka K, Kondo M, et al. The JAK inhibitor, tofacitinib, reduces the T cell stimulatory capacity of human monocyte-derived dendritic cells. *Ann Rheum Dis*. 2014;73:2192–2198.
14. Bhol KC, Dans MJ, Simmons RK, Foster CS, Giancotti FG, Ahmed AR. The autoantibodies to alpha 6 beta 4 integrin of patients affected by ocular cicatricial pemphigoid recognize predominantly epitopes within the large cytoplasmic domain of human beta 4. *J Immunol*. 2000;165:2824–2829.
15. Suelves AM, Zhao TZ, Siddique SS, Foster CS. Profile of local interleukin expression in a cohort of ocular cicatricial pemphigoid patients. *Invest Ophthalmol Vis Sci*. 2012; 53:8112–8117.
16. Sarny S, Hucke M, El-Shabrawi Y. Treatment of mucous membrane pemphigoid with Janus kinase inhibitor baricitinib. *JAMA Ophthalmol*. 2018;136:1420–1422.
17. Munyangango EM, Le Roux-Villet C, Doan S, et al. Oral cyclophosphamide without corticosteroids to treat mucous membrane pemphigoid. *Br J Dermatol*. 2013;168: 381–390.
18. Choy EH. Clinical significance of Janus Kinase inhibitor selectivity. *Rheumatology*. 2019;58:953–962.
19. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med*. 2017;376:652–662.
20. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis Rheum*. 2019;71:1788–1800.
21. Genovese MC, Kalunian K, Gottenberg JE, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. *J Am Med Assoc*. 2019;322:315–325.
22. Paley MA, Karacal H, Rao PK, Margolis TP, Miner JJ. Tofacitinib for refractory uveitis and scleritis. *Am J Ophthalmol Case Rep*. 2019;13:53–55.
23. Bauermann P, Heiligenhaus A, Heinz C. Effect of Janus kinase inhibitor treatment on anterior uveitis and associated macular edema in an adult patient with juvenile idiopathic arthritis. *Ocul Immunol Inflamm*. 2019;27:1232–1234.
24. Miserocchi E, Giuffre C, Cornalba M, Pontikaki I, Cimaz R. JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis. *Clin Rheumatol*. 2020;39: 847–851.