Anti-interleukin-6 receptor therapy with tocilizumab for refractory pseudophakic cystoid macular edema

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ABSTRACT

Purpose: To describe the clinical course of a patient with refractory pseudophakic cystoid macular edema treated with interleukin-6 receptor antagonist tocilizumab.

Observations: An 80-year-old Caucasian man with past ocular history significant for glaucoma (right eye) and iritis presented with cystoid macular edema (CME) in the right eye (OD). His ocular surgery history was significant for cataract extraction with posterior chamber intraocular lenses in 1999 and YAG laser capsulotomy in 2014 in both eyes (OU). His medications at time of presentation included latanoprost and dorzolamide-timolol in OD for glaucoma, as well as prednisolone in OD for iritis. Upon examination, his visual acuity was 20/250 in OD and 20/20 in the left eye (OS). Slit-lamp examination revealed no cells or flare in OU. Dilated fundus exam showed CME and a cup-to-disk ratio of 0.9 in OD and normal findings in OS. Initial spectral domain optical coherence tomography (SD-OCT) demonstrated intraretinal fluid in both outer and inner layers as well as mild subretinal fluid with an intact ellipsoid zone in OD. Fluorescein angiography revealed perifoveal leakage in OD. Laboratory evaluations, including infectious work-up, were unremarkable. While the patient's CME initially improved after initiation of therapy with topical prednisolone and oral acetazolamide, the CME later recurred after systemic acetazolamide was stopped due to intolerable side effects. Despite multiple therapeutic approaches, including topical and systemic corticosteroids (both oral and intravenous) and topical interferon α2b over the course of more than one year, the patient's visual acuity continued to worsen with increasing intra- and subretinal fluid in the macula. Due to the refractory CME, the patient was started on monthly infusions of anti-interleukin (IL)-6 receptor tocilizumab (8 mg/kg) with three days of methylprednisolone infusions (500 mg/day). After nine cycles of treatment, SD-OCT demonstrated restoration of normal foveal contour with complete resolution of CME.

Conclusions and Importance: IL-6 inhibition with tocilizumab may be a safe and effective treatment for refractory CME. Further studies are needed to elucidate the nature and extent of therapeutic IL-6 inhibition in CME.

1. Introduction

Cystoid macular edema (CME) is characterized by disruption of the normal blood-retinal barrier (BRB). Increased vascular permeability from perifoveal retinal capillaries allows fluid to accumulate within the intracellular spaces of the retina, such as the outer plexiform and inner nuclear layers. Over time, intra- and subretinal fluid accumulation can lead to visual loss. Possible causes of CME are diverse and varied, including structural (e.g. diabetes, retinal vein occlusion), inflammatory (e.g. uveitis, Irvine-Gass syndrome), tractional (e.g. vitreomacular traction), dystrophic (e.g. retinitis pigmentosa), and medication-related factors (e.g. prostaglandins, epinephrine).

CME often presents with symptoms such as decreased visual acuity, metamorphopsia, central scotomas, and loss of color vision or contrast

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sensitivity. Slit lamp examination often shows retinal thickening and loss of normal foveal contour. In severe or chronic cases, other findings such as optic disc edema, lamellar hole, or splinter hemorrhages may be present. The gold standard for diagnosis is fluorescein angiography (FA), which shows perifoveal capillary leakage and dilatation. Other modalities, such as visual acuity and spectral domain optical coherence tomography (SD-OCT), are routinely used to monitor disease progression. SD-OCT shows retinal thickening, loss of foveal contour, and cystic macular hyporeflectivity in CME.

In some patients, CME can occur as a complication of cataract surgery. Despite advancements in phacoemulsification and small incision cataract surgery, pseudophakic cystoid macular edema (PCME), or Irvine-Gass syndrome, remains a common postoperative complication of cataract surgery. PCME is characterized by disruption of the normal blood-retinal barrier due to upregulation of inflammatory mediators secondary to surgical manipulation. PCME typically develops about four to six weeks post-cataract surgery, though in some patients, it can also develop months to years after surgery. Unfortunately, slit lamp examination alone can miss up to 5–10% of cases of PCME; thus, additional evaluation with ancillary imaging modalities is crucial.

While most cases of acute PCME resolve spontaneously, some cases can be persistent and present a challenge to physicians due to lack of standardized and effective treatment protocols. If left untreated, chronic CME can lead to severe central vision loss due to distortion of photoreceptor architecture from retinal thickening and fluid collection. Topical NSAIDs and corticosteroids have been used for some time to treat PCME, but long-term data on their efficacy are limited. More recently, other studies have examined the use of immunomodulatory therapy (IMT), such as tumor necrosis factor (TNF)-α inhibitors and interferon (IFN)-α for CME. An interventional retrospective study from the Pan-American Collaborative Retina Study Group, for example, found that seven cases of refractory PCME achieved excellent six-month outcomes after a single intravitreal injection of infliximab (0.5 mg/0.05 mL), while a separate study investigating the use of intravitreal infliximab in patients with refractory diabetic macular edema or neovascular age-related macular degeneration found significant drug-related adverse effects and no improvement in visual acuity or resolution of CME. Deuter et al. first reported that in three patients with refractory PCME, IFN-α therapy (3 million IU/day) led to resolution of CME within four weeks of treatment with subcutaneous IFN-α without significant adverse effects. Maleki et al. later reported that CME significantly improved after four weeks of treatment with topical interferon α2b (1 MIU/ml) four times a day, and completely resolved after twelve weeks, in a patient with PCME.

Other types of IMT, including interleukin (IL)-6 inhibition with tocilizumab, have been examined in the treatment of CME. For example, Adán et al. reported the use of tocilizumab infusions for the treatment for refractory uveitis-related CME, and more recent studies noted efficacy of anti-IL-6 therapy in chronic CME of other etiologies. We herein report a case of a patient with chronic CME concerning for Irvine-Gass syndrome that had been refractory to treatment with systemic carbonic anhydrase inhibition, topical and oral corticosteroids, and topical interferon α2b who showed significant anatomical improvement while on monthly anti-IL-6 tocilizumab infusions.

2. Case report

An 80-year-old Caucasian man presented to our tertiary Uveitis Clinic in August 2018 by referral for further evaluation due to worsening vision in right eye (OD) for one month. His ocular surgery history was significant for cataract extraction with posterior chamber intraocular lenses in 1999 and YAG laser capsulotomy in 2014 in both eyes (OU). His ocular history was significant for advanced glaucoma in OD, blepharitis with keratitis, and possible history of iritis in OD diagnosed in 2018. Family history and detailed review of systems were noncontributory. The patient had no history of otherwise relevant systemic illnesses, including diabetes mellitus. Current medications included latanoprost one time per day and dorzolamide-timolol twice per day in OD for glaucoma, as well as prednisolone six times per day in OD for iritis (diagnosed two months prior to presentation).

On examination, the Snellen best-corrected visual acuity (BCVA) was 20/250 in OD and 20/20 in left eye (OS). Intraocular pressure (IOP) was 20 mmHg in OD and 10 mmHg in OS. Slit-lamp examination of the anterior chamber revealed no cells or flare in OU. Posterior examination revealed CME and advanced optic disc cupping (cup-to-disc ratio: 0.9) in OD, and normal appearance in OS (Fig. 1A). Fluorescein angiography (FA) showed peri-foveal leakage without macular and retinal ischemia in OD, and normal transit in OS (Fig. 1G). SD-OCT revealed presence of intra- and subretinal fluid in OD and mild epiretinal membranes in OU (Fig. 1C and D). Initial work-up, including complete blood count, complete chemistry panel, urinalysis, syphilis, herpes simplex virus (HSV), varicella zoster virus (VZV), angiotensin-converting enzyme, human leukocyte antigen (HLA)-B27, and chest X-ray, were conducted and were all negative or within normal limits.

The patient was diagnosed with persistent CME in OD with concern for multiple possible etiologies, including PCME, severe glaucoma, latanoprost, YAG laser capsulotomy, iritis, and possible masquerade syndrome given chronic course. Latanoprost was discontinued and oral acetazolamide was started, and topical prednisolone 1% was tapered due to the lack of intraocular inflammation. Two months later, fundus exam and OCT showed resolution of CME in OD (Fig. 2B), with improvement of BCVA to 20/50. However, five months after starting therapy, the patient needed to stop acetazolamide due to intolerable side effects, including severe gastrointestinal distress and persistent tingling sensations in the distal extremities. His BCVA and OCT were stable at that time (Fig. 2C). His IOP was 8 mm Hg.

Two months later in March 2019, the patient noticed a shadow in OD that gradually worsened. On examination, BCVA had dropped to 20/400 in OD. SD-OCT showed recurrence of intra- and subretinal fluid in OD (Fig. 2D) without evidence of ocular inflammation. The patient was started on oral prednisone (30 mg/day) and topical prednisolone 1% four times a day in OD. Despite two months of systemic steroid treatment, SD-OCT showed worsening of CME (Fig. 2E). At that time, the patient was started on topical IFN α2b (1 MIU/ml) four times a day.

At the three-month follow-up in August 2019, the patient noted no visual improvement. Snellen BCVA at the time remained 20/400 in OD and SD-OCT showed continued worsening CME and subretinal fluid (Fig. 2F). Masquerade syndrome was considered as a possibility, and diagnostic vitrectomy was performed to rule out other possible causes of persistent CME, including intraocular lymphoma. However, cytocritic evaluation and flow cytometry found no evidence of malignant cells, and no abnormalities in B-cell clonality, MyD88 mutation, and VH hypermutation were found.

One month after diagnostic vitrectomy, the CME remain unchanged (images not shown). Discussion was made regarding alternative treatment options for refractory CME, and the patient agreed to begin monthly infusions of tocilizumab (TCZ), an IL-6 inhibitor, at the dose of 8 mg/kg. With each cycle, the patient received 3 days of infusions of methylprednisolone 500 mg per day. At the four-month follow-up after four cycles of treatment, SD-OCT demonstrated resolution of normal foveal contour with complete resolution of CME (Fig. 2G). IOP remained stable in OU. At the nine-month follow-up, SD-OCT showed continued preserved foveal contour without any evidence of CME (Fig. 2H), and BCVA in OD improved significantly from 20/400 to 20/60.
3. Discussion

3.1. Generating a diagnosis

We have presented a case of an 80-year-old male with a history of cataract surgery who later developed CME that was refractory to multiple treatments. The etiology of the patient’s CME was not initially clear. The differential diagnosis for CME includes retinal and choroidal vascular diseases, postoperative inflammation, non-infectious and infectious uveitis, medication-induced CME, retinal dystrophies, anatomical abnormalities, and neoplasms. In our particular patient, factors that could contribute to CME in OD included his history of cataract surgery in 1999, YAG capsulotomy in 2014, iritis in 2018, and use of topical latanoprost for his glaucoma, as well as the presence of an ERM. Masquerade syndrome was also suspected given the chronic course, but diagnostic vitrectomy showed no evidence of malignancy. Given that the patient never had any evidence of anterior chamber inflammation during our monitoring of him, we felt that latanoprost was unlikely to be the cause of his CME. The patient’s possible history of iritis was unclear based on previous records. Because the patient never showed any signs of inflammation in the anterior or vitreous chamber during the entire duration of our follow-up, uveitic macular edema (UME) was felt to be less likely a sole contributing factor for the chronic refractory CME. While both a history of cataract surgery and YAG capsulotomy could contribute to his CME, given the timeline, YAG capsulotomy seemed less likely owing to clinical history. Moreover, CME typically occurs in the

Fig. 1. Wide-field fundus photographs of the right (A) and left (B) eyes showing clear media and no apparent retinal lesions. SD-OCT horizontal cross-sections through the fovea of the right eye (C) showing intraretinal fluid accumulation and of the left eye (D) showing normal anatomy. Early and late fundus angiography of the right eye (E and G) showing peri-foveal leakage without vessel leakage and of the left eye (F and H) showing normal vasculature.
weeks to months post-procedurally, whereas cataract surgery has been known to cause CME in the months to years following surgery. Furthermore, certain cases of post-surgical PCME, if refractory to conventional treatment or sub-therapeutically managed, can persist for many years after cataract surgery.

In this case, there were no systemic manifestations or abnormalities in blood evaluation to suggest a systemic or infectious etiology. The initial response to acetazolamide provided further support for excluding traction caused by ERM as a possible cause. Given the occurrence of this patient’s CME in the context of his history of cataract surgery and possible iritis, in conjunction with the exclusion of other possibilities, this patient was diagnosed with persistent CME concerning for Irvine-Gass syndrome, with less likelihood for uveitic macular edema (UME).

![Fig. 2. SD-OCT of the right (OD) and left (OS) eyes. Before oral acetazolamide (row A); after 2 months of acetazolamide (row B); after 5 months at which time oral acetazolamide was stopped due to side effects (row C); after 7 months at which time oral prednisone was started due to recurrence of CME (row D); after 9 months at which time oral prednisone was tapered, latanoprost was discontinued, and IFN-α2b was started (row E); after 12 months, at which time IFN-α2b was stopped, diagnostic vitrectomy was performed to rule out masquerade syndrome, and TCZ was eventually started (row F); after 4 cycles of TCZ and methylprednisolone infusions (row G); and after 9 cycles of TCZ and methylprednisolone infusion (row H).]
3.2. Current treatments for PCME and UME

Most patients with clinical PCME typically improve spontaneously within 3–12 months after symptom onset.22 While such data may be welcome news for most patients prognostically, it also explains the lack of robust randomized clinical trials on therapeutic interventions for refractory PCME. Treatment for UME is slightly different, in which the most important principle is to ensure that the uveitis, including subclinical inflammation, and any underlying systemic diseases are completely controlled. Macular edema can be seen in quiescent uveitic eyes and pose therapeutic challenges, as the macular edema is often chronic and associated with irreversible BRB damage. Currently, no standardized protocols exist for treating refractory PCME or UME. Therapies for CME include NSAIDs, corticosteroids, anti-VEGF treatments, carbonic anhydrate inhibitors, and immunomodulatory therapy. Surgery with laser vitreolysis and pars plana vitrectomy may be indicated in cases that are refractory to conventional medical therapies.

NSAIDs and corticosteroids work by inhibiting cyclooxygenase and phospholipase A2, respectively, thereby decreasing prostaglandin levels and reducing ocular inflammation. In a comprehensive review of 82 publications from 1974 to 2018 on the role of steroids and NSAIDs in preventing and treating PCME, the authors concluded that while corticosteroids remained the mainstay for PCME therapy, the combination of topical steroids with adjuvant NSAIDs could prevent PCME in uncomplicated cataract surgery.23 However, there is limited to no role for topical NSAID monotherapy in the treatment of inflammatory ME.24 and no recent large studies have investigated NSAIDs as sole treatment for chronic CME. Because of the available scientific data, in conjunction with the fact that the etiology of our patient’s macular edema may have had a uveitic component in addition to PCME, we chose not to pursue the NSAID treatment option for our patient. Corticosteroids, commonly used for PCME and UME, can be administered topically, perioricularly, intravitreally, or systemically. Few recent large randomized clinical trials have examined the relative efficacies of these different routes of delivery of steroids for PCME. Given that our patient’s CME continued to worsen despite treatment with both topical and systemic corticosteroid therapy, we felt the need to escalate the patient to a different level of therapy.

Oral carbonic anhydrase inhibitors and anti-vascular endothelial growth factor (VEGF) therapy have also been employed for the treatment of refractory PCME and UME. Various groups have used acetazolamide to successfully treat PCME and UME,25,26 Similar to our own case, one study reported rapid improvement in visual acuity after beginning oral acetazolamide treatment with recurrence of CME after discontinuation.22 While small studies and case reports have showed promising results with the use of oral carbonic anhydrase inhibitors, their use can often be limited by a relatively severe side effect profile, as was the case for our patient. In fact, in a study of 10 patients with refractory CME randomized to either acetazolamide or placebo, only 1 of the 5 patients randomized to receive acetazolamide was able to tolerate and complete the 4-week course.22 In our case, oral acetazolamide likely contributed to the patient’s initial improvement of CME. Unfortunately, the patient was unable to continue this therapy due to intolerable side effects. Currently, there are no reports in the literature about the efficacy of topical carbonic anhydrase inhibitors for refractory PCME.

Literature on the efficacy of VEGF inhibitors in the treatment of PCME and UME has been conflicting. In a series of 16 eyes with refractory PCME, patients who received 1.25 mg of intravitreal bevacizumab did not show improved visual outcomes.20 In other studies, intravitreal ranibizumab and bevacizumab improved visual outcomes in patients with UME refractory to corticosteroid treatment.30–32 However, in a randomized clinical trial comparing intravitreal bevacizumab to intravitreal triamcinolone (IVTA) for refractory UME, patients with IVTA therapy showed better control of leakage and reduced central subfield macular thickness (CSMT) compared to patients with anti-VEGF therapy.33 We knew that the transient nature of intravitreal injections would require repeated injections, with no guarantee of long-term therapeutic benefit. For these reasons, after discussion with the patient, we felt that alternative treatment modalities could be explored, such as IMT with IL-6 inhibitors.

Due to the lack of robust randomized trials, refractory PCME remains difficult to treat. Previous reports have shown benefit with anti-TNF-α inhibitors11,12 and IFN-α therapy13,14 but have been restricted to isolated case studies. Most studies on immunosuppressive agents with antimetabolites such as methotrexate, azathioprine, or mycophenolate are focused on controlling active ocular inflammation rather than UME. One recent study investigated the role of mycophenolate specifically in UME. Patients were separated into those with preexisting ME and those with new onset ME during standard mycophenolate treatment. It demonstrated that ME could develop in up to 39% of patients on active mycophenolate treatment and that mycophenolate alone is not always sufficient in treating or preventing UME.15 Additional immunomodulatory therapeutic agents, including anti-IL-6 tocilizumab, have been studied,15–18 but these reports have been limited to cases of cystoid macular edema that occurred outside the context of post-cataract surgery. To the best of our knowledge, this is the first published case of a patient with refractory CME concerning for Irvine-Gass syndrome treated with anti-IL-6 therapy using tocilizumab.

3.3. What is tocilizumab and why did we begin this treatment?

Tocilizumab is a humanized monoclonal antibody administered by intravenous infusions or subcutaneous injection for the treatment of various autoimmune disorders, including rheumatoid arthritis and juvenile idiopathic arthritis. Tocilizumab recognizes the IL-6 binding site of IL-6R and competitively inhibits IL-6 signaling. IL-6 is a pro-inflammatory cytokine produced by T cells and monocytes that mediates the acute phase response by enhancing vascular permeability and inducing cellular proliferation and differentiation. Persistent production is implicated in autoimmunity and chronic inflammation.

Previous studies have shown that elevated levels of certain cytokines, including IL-6, in the aqueous humor correlate positively with foveal center point thickness in patients with cystoid macular edema after cataract surgery.34 Adam et al. reported the use of tocilizumab infusions for the treatment for refractory uveitis-related cystoid macular edema.15 More recent studies noted efficacy of anti-IL-6R therapy in chronic cystoid macular edema secondary to other etiologies.16–18 In a multicenter study of patients with refractory and noninfectious uveitic CME, treatment with TCZ showed a statistically significant reduction in macular thickness (432.7 ± 161.8 μm vs 259.1 ± 49.5 μm; p < 0.0001). Moreover, 21 of 23 eyes (91%) showed reduction in number of anterior chamber cells after 12 months of TCZ therapy, and resolution of vitritis was observed in 19 of 27 eyes (70.3%).35 In the STOP-UVEITIS study, an open-label and prospective randomized trial, infusion of tocilizumab at a dose of 4 or 8 mg/kg every four weeks for six months to treat active uveitis was effective in improving visual acuity, reducing central macular thickness (−83.88 ± 136.1 μm at month 6; p < 0.01), and improving vitreous haze (10 out of 23 subjects demonstrated a ≥ 2-step decrease in vitreous haze at month 6).19

Given these data, our patient was started on tocilizumab, with the understanding that nonresponse could be an indication for further medical or surgical intervention. After our patient failed therapy with topical interferon α2b, we chose not to begin therapy with TNF-α inhibitors, such as infliximab and adalimumab, due to their potential side effect profile, including drug-induced hepatotoxicity, congestive heart failure, infections, and demyelinating disease, as well as in the context of our patient’s older age. The safety profile of tocilizumab has been well described in several studies, including the STOP-UVEITIS study.36 While a transient, dose-dependent neutropenia, attributed to peripheral margination, has been reported, Nishimoto and associates, who evaluated the safety of tocilizumab for patients with rheumatoid arthritis in a meta-analysis, found no association between low absolute neutrophil...
count and neutropenic sepsis. While we recognized these potential side effects, we chose to start our patient on the higher dose of tocilizumab (8 mg/kg) due to the severe nature of his CME that had been refractory to multiple therapeutic approaches, including topical and oral corticosteroids and topical interferon α2b, over the course of more than one year. Given the severity of our patient’s CME, we also chose to begin concomitant therapy with methylprednisolone infusions with each cycle to allow for possible synergistic effects, though tocilizumab monotherapy has also shown efficacy for CME in previous studies. While methylprednisolone may certainly have played a role in reducing the CME, given that the patient had not responded to prednisone 30mg/day for an extensive period of time previously, we felt that methylprednisolone alone was not responsible for the complete CME resolution. Instead, we suspect that TCZ and methylprednisolone may, in combination, be able to treat chronic CME synergistically. Immuno-modulatory therapies, such as tocilizumab, have been developed to address the risks and complications associated with long-term and high-dose steroid use. Due to limited follow-up and inadequate sample size, this report provides minimal insights into long-term advantages and disadvantages of tocilizumab treatment. Studies to date have not shown geriatric-specific adverse effects with tocilizumab that would limit the usefulness of this treatment in elderly populations, though caution must be exercised in all patients regardless of age to decrease the risk of infection. Our patient tolerated monthly infusions of TCZ and methylprednisolone and achieved resolution of intra- and subretinal fluid on SD-OCT. The CME improved significantly in our patient, with restoration of foveal contour on SD-OCT; his vision in OD also improved significantly from 20/400 to 20/60 at 9-month follow up.

4. Conclusions

Patients with a long-standing history of refractory CME who do not respond to conventional therapeutic agents may benefit from the use of tocilizumab, even decades after cataract surgery, as a safe and effective alternative treatment option. Prompt administration in certain cases can lead to additional functional and anatomical improvement. Based on the patient’s unresponsive CME that worsened over four months before anti-IL-6 therapy, his recovery is much more likely to be related to tocilizumab than spontaneous resolution. Our findings also suggest that IL-6 may play a significant pathogenic role in the perpetuation of chronic CME refractory to traditional therapies. Additional studies, including randomized controlled trials, are required to fully elucidate the nature and extent of therapeutic IL-6 inhibition in chronic and refractive CME.

Patient consent

Written informed consent was obtained from the patient for the publication of this manuscript.

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Authorship

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

Declaration of competing interest

All authors declare that there are no conflicts of interest related to this report.

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