

Emerging therapies for the treatment of uveitis: clinical trial observations

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Uveitis, a leading cause of blindness in the USA and western Europe, can pose a challenge to ophthalmologists when considering treatment modality. Although once considered acceptable, corticosteroid monotherapy is no longer alone at the head of treatment options. Newer, more specific treatments, and medications translated from other divisions of medicine comprise the new wave of therapy employed by uveitis practitioners around the world, with and without regulatory approval. The purpose of this review is to examine the current status of clinical trial observations for newer treatments for uveitis. Innovative corticosteroid therapies and methods of delivery are described, in addition to novel calcineurin inhibitors, new biologic response modifiers, and other emerging therapies. Although very few therapies are approved for use explicitly in uveitis, the reported results of clinical trials are examined. A concise overview of the ongoing challenges in clinical research is discussed, from the perspective of the uveitis specialist, and the patient. Direction for the future of drug development and use is both exciting and dire, as these treatments are the only pathway for patients seeking to preserve vision.

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Uveitis is widely cited as a leading cause of preventable blindness, accounting for 10–15% of all cases of blindness [1]. Most ophthalmologists rely heavily on corticosteroid (CS) use in various forms to control eye inflammation. But chronic or repeated CS monotherapy has been documented, in many long-term outcomes studies, to result in loss of vision secondary to the inflammatory disease itself or to complications from the CSs. Thus, the standard of care which has evolved over the past 40 years is one which embraces the employment of steroid-spare immunomodulatory therapy (IMT). Targets of immune modulation include, in order of least to most aggressive, nonsteroidal anti-inflammatory agents, antimetabolites, calcineurin inhibitors, biologic response modifiers and cytotoxic agents. Very few drugs of all mentioned classes have undergone the rigorous requirements necessary to achieve US FDA approval for on-label use explicitly for the indication of treating uveitis; current practice is largely based on clinicians' years of experience and smaller-scale studies. Fortunately, given the complexity of uveitic targets, some pharmacologies approved for use in other indications are readily adaptable for use in uveitis.

The purpose of this review is to examine the current status of clinical trial observations for newer treatments for uveitis.

Recent advances in CS therapy

CS use has been and remains the mainstay of treatment for many cases of uveitis [2]. Generally, CS offers treatment at low cost for high yield and quick results

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in controlling inflammation. Problems always arise in moderate- to long-term use of CS, however, forcing ophthalmologists to weigh the risks and benefits on a case-by-case basis. Recent developments in CS use and application have been focused on improved quality of life for patients, be it decreased frequency of application, as is the case with difluprednate, or foregoing patient application completely, as in the drug-eluting devices. Impressive results in safety and efficacy in inflammation control leads to the recommendation that these CS therapies be considered as adjuvant to IMT, allowing the best chances of achieving sustained remission, someday completely CS-free [3].

■ Durezol® (difluprednate ophthalmic emulsion)

According to FDA documentation, Alcon Research achieved approval for their topical CS, Durezol®, for use in the additional indication, endogenous anterior uveitis, on 13 June 2012 [4]. Its primary indication for postoperative inflammation and pain was tested in a multicenter, placebo-controlled trial across the USA [5]. Eligible patients, that is those who had recently undergone unilateral ocular surgery ($n = 438$), were randomized to three treatment arms: durezol once daily, durezol twice daily (b.i.d.) and placebo; the primary outcome measure was presence of anterior chamber inflammation, and the secondary outcome measures included pain and reported adverse events [5]. The study found that “difluprednate given 2 or 4 times a day cleared postoperative inflammation and reduced pain rapidly and effectively”, and FDA approval followed, with difluprednate becoming the first topical CS approved for pain alleviation [5,6]. A later study by Smith and colleagues reaffirmed this finding. They tested initiation of difluprednate b.i.d. 24 h before surgery, and two weeks after, followed by a slow taper in 121 patients [6]. Using similar primary end points of anterior chamber inflammation based on cell-grading and haze, they found that 74.7% of patients randomized to the difluprednate group were inflammation-free by day 14, as compared with 42.5% of patients using placebo ($p < 0.001$) [6]. By day 28, 89.9% of those using difluprednate were inflammation-free and tapering the medication, as compared with 52.5% of those randomized to the placebo group ($p = 0.0001$) [6]. In showing equal efficacy between b.i.d. dosing and four-times daily dosing, Smith and colleagues provided support for less frequent application, possibly leading to a lower incidence of side effects and associated sequelae, such as transient elevated intraocular pressure (IOP); the latter study reported this in three subjects randomized to the experimental group [6].

Follow-up studies, one pertaining to diabetic macular edema (DME), and one pertaining to endogenous

anterior uveitis followed the favorable results of the first studies on Durezol. Nakano and associates tested the efficacy of Durezol against sub-tenon triamcinolone in 17 patients (22 eyes) with persistent DME [7]. Primary outcomes were based on visual acuity improvement; in comparing the difluprednate patients and the sub-tenon triamcinolone patients, there existed no statistically significant difference in improvement rate in visual acuity [7]. Differences in optical coherence tomography measures were also found to not differ statistically [7]. For patients desiring a less-invasive treatment method for edema, this study was of key importance. The researchers concluded that Durezol appears to be safe and as effective as the current standard of therapy for DME, in addition to being readily available and noninvasive, as compared with sub-tenon triamcinolone. In a multicenter, randomized, double-masked trial with 90 participants experiencing active, anterior noninfectious uveitis, researchers aimed to compare difluprednate to the current standard of care, topical prednisolone acetate 1%, using anterior chamber inflammation via cell grading as a primary outcome measure [8]. Using a two-bottled dosing system to ensure masking, researchers randomized patients in a 1:1 ratio of four- or eight-times daily dosing for difluprednate or prednisolone acetate 1%, respectively. Follow-up was scheduled at days 3, 7, 14, 21, 28, 35 and 42 [8]. In their noninferiority analysis, Foster and associates concluded that difluprednate once daily was as effective as prednisolone acetate 1% eight-times daily in treating endogenous anterior uveitis [8]. Anterior chamber cell (ACC) counts and grade, anterior chamber flare, posterior synechiae, peripheral anterior synechiae, hypopyon, keratic precipitates and limbal injection were all measured via slit lamp examination [8]. Subjective assessments were also collected, and included eye pain, photophobia, blurred vision, lacrimation, overall quality of life and work limitations [8]. More patients randomized to the prednisolone acetate 1% arm were forced to discontinue the study secondary to investigator-determined lack of therapeutic efficacy, as compared with patients randomized to the difluprednate arm [8]. Overall, a decrease in ACCs of < 0.5 units from baseline was seen in the patients using difluprednate, fulfilling the primary end point of the study; patients enrolled experienced mean ACC improvements of 2.1, compared with 1.9 step grading in the difluprednate and prednisolone acetate 1% cohorts, respectively [8]. Furthermore, at and after every timepoint past day 7, difluprednate was seen to be more effective in treating baseline ACC levels, and also superior in improving best-corrected visual acuity (BCVA) [8]. Total subjective symptom improvement was reported to be higher

in the difluprednate group [8]. Finally, in accord with the first set of trials, increased IOP was reported in six patients randomized to the difluprednate cohort, and was the principal adverse event reported; however, no difference in reported rates of increased IOP existed between randomized groups [8].

Clinical trials relating to the safety and efficacy of Durezol prove to be promising for patients and physicians seeking less frequent dosing, higher patient compliance, and perhaps, less invasive methods of inflammation control in the anterior chamber.

■ Drug delivery implants

Despite the strength and efficacy of new and existing topical CS, the difficulty in reaching intermediate and posterior locations of inflammation greatly limits their use in many cases of uveitis [1]. Recent advances in local CS delivery, outside of the traditional injectable route, have reopened this door as an option for patients, particularly those who experience unilateral disease, or who have an aversion to systemic medications (such as pregnant and breastfeeding women, or individuals with serious comorbidities). Additionally, newer therapies are employing longer-acting CS, allowing for less-frequent administration (as compared with the typical administration schedule of triamcinolone once every 1–4 months).

Ozurdex[®] (dexamethasone drug delivery system) is an intravitreal implantable device of 700 µg of preservative-free dexamethasone approved for use in noninfectious posterior uveitis [9]. Dexamethasone has been touted as a “far more muscular ocular CS” than past formulations used intravitreally and transseptally, thereby affording the patient inflammation control through high initial therapeutic concentrations, followed by a steady, sustained release of medication over a six-month period [9]. The Phase III, randomized, sham-controlled, 26-week study included 229 eyes with noninfectious, intermediate or posterior uveitis. Participants were divided into three arms with differing dosages [10]. Inclusion in the study was contingent upon the presence of vitreous haze scored at or above 1.5+ and a BCVA score between 20/630 and 20/32; uncontrolled glaucoma and ocular infection were exclusionary [10]. Also, topical and systemic CSs at stable, unchanged dosages were allowed throughout the study [10]. Vitreous haze evaluation at 8 weeks was a key indicator of success; both the 700-µg cohort and the 350-µg cohort showed statistically significantly less inflammation as compared with the placebo group, decreased from scores of, on average 2+ haze universally at onset [10]. Complete vitreous haze control was seen in approximately 22 patients in the 700-µg experimental group as early as week 3, with rising numbers

of participants reaching scores of 0 vitreous haze as the follow-up progressed. Over 90% of participants in the 700-µg experimental group achieved a score of 0 vitreous haze at week 6 [9,10]. Investigators also reported a mean improvement of BCVA in the implant groups over the sham group throughout the study period [10]. Quality of life measures were also found to be more favorable in the two experimental cohorts as compared with the sham group, and as evaluated by the National Eye Institute Visual Functioning Questionnaire-25 [9]. Safety evaluation of the implant revealed increases in IOP, cataract development, conjunctival hemorrhage, ocular discomfort and eye pain, and active anterior uveitis, although none of these occurred at statistically significantly different rates among the three groups [10].

An additional study conducted confirmed many of the above results, but shifted focus toward macular edema associated with uveitis, as the primary indication for Ozurdex use was macular edema following retinal vein occlusion. Williams *et al.* evaluated 41 eyes of patients with persistent macular edema attributed to uveitis; a single-blinded study randomized patients into similar dosage groups as outlined above [11]. Assessment of BCVA and vascular leakage as evaluated by fluorescein angiography revealed statistically significantly better outcomes in the 700-µg experimental group, as compared with the placebo group (observation only) [11]. Adverse event findings were also reinforced, as 38.5% of eyes randomized to the 700-µg experimental group experienced elevated IOP (however these cases were not deemed serious, and were topically treated) [11].

The Retisert[™] implant (fluocinolone acetonide intravitreal implant) similarly delivers 0.59 mg of drug at sustained rates of release, with a higher loading dose, followed by a steady rate of delivery for 30 months [12]. In the original pilot study, five eyes of four patients with noninfectious, posterior segment disease were included [13]. Four out of five eyes received a 2.1 mg device and were followed for an average of 57.4 months, with visits occurring, at most, every 3 months [13]. A total of 28 additional patients (31 eyes) were subsequently enrolled in study, and randomized to either a 0.59- or 2.1-mg implanted device, with a 0.6- or 2.0-µg/day release rate, respectively [13]. Cases of uveitis exhibiting a partial response to oral, local, or systemic CS and/or IMT were targeted for enrollment; the number of inflammatory recurrences served as the primary end point [13]. Prior to implantation, an average of 2.5 inflammatory recurrences was reported [13]. In the periods of 0–6 months, 0–12 months and 0–24 months, zero inflammatory recurrences were reported in the study eye; one inflammatory recurrence was reported

at month 29, one at month 33, and two additional inflammatory recurrences beyond 33 months of follow-up (although 15 eyes did not reach past 24 months of follow-up) [13]. Result in the fellow eyes were not as favorable; as an example, nine out of 23 eyes reaching the 24-month follow-up timepoint experienced an inflammatory recurrence in the fellow eye [13]. Visual acuity improvement was reported, in addition to steadily decreasing usage and dosage of systemic IMT, and local and topical CS [13]. Elevated IOP was cited as the most common adverse event, and retinal detachment occurred in two eyes [13].

Two large-scale, prospective, dose-masked and dose-randomized, controlled trials followed these initial promising results; the first, a three year endeavor, enrolled 278 patients across 26 centers, and the second, also three years in duration, enrolled 147 patients across 37 study centers [14–16]. Patients were initially randomized to a 0.59- or 2.1-mg dose in a 1:1 ratio; inclusion criteria included age 6 and above, and use of systemic CS, local CS or systemic IMT, while uncontrolled glaucoma and infectious forms of posterior uveitis were exclusionary [14]. Only one eye, the one deemed as having more severe disease, was chosen for implantation [14]. Recurrence rates of intraocular inflammation 34 weeks prior and 34 weeks after implantation were compared separately, and between the groups, serving as the primary efficacy outcome [14]. The recurrence rate before and after did not statistically significantly differ between the groups; impressively, the recurrence rate decreased 51.4–6.1% overall [14]. Fellow eye recurrence was reported to have significantly increased [14]. Other adverse events included increase in baseline IOP, requiring ocular hypertensives and/or surgical intervention; increase in lens opacity, necessitating cataract surgery; eye pain; hypotony; and explantation [14]. The finalized analysis expanded the primary efficacy outcome to 1 year prior, and 3 years postimplantation for calculation of inflammatory recurrence rate [15]. Researchers found dramatic decreases in recurrence overall (initially 58–62%), with the lowest reported rates at year 1 (4–7%), with slightly higher rates of recurrence at year 2 (10–17%) and higher still at year 3 (20–41%) [15]. The final results also confirmed the initial findings of increased recurrence in the fellow eye, and found no statistically significant differences between the dosing groups, with respect to risk of uveitis recurrence [15]. A total of 98% of study eyes and 86% of fellow eyes reported some ocular adverse event; in addition to those above, conjunctival hyperemia, conjunctival hemorrhage, blurred vision, reduced visual acuity, floaters, retinal detachment, and other complications requiring explantation were also reported [15]. The

second study aimed to compare the fluocinolone acetonide implant to systemic therapy, utilizing time to first inflammation recurrence as the primary outcome measure [16]. ‘Standard of care’ systemic therapy was employed as the comparator, and included systemic CS and approved IMTs at set dosages and taper schedules [16]. The average number of postoperative recurrences was statistically significantly lower in the implant group, as compared with the systemic therapy group (0.3 vs 1.2, respectively); up to six recurrences were reported in the systemic therapy group, while one recurrence was the maximum reported in the implant group [16]. A significantly higher number of serious adverse events and adverse events were reported in the implanted study eyes, however, with over 20% requiring surgical intervention, confirming results described above [16].

The Multicenter Uveitis Steroid Treatment Trial similarly aimed to evaluate the relative effectiveness of systemic CS and IMT against the fluocinolone acetonide implant among 255 patients over 24 months, with improvement in BCVA serving as the primary outcome measure [17]. The study found that both groups exhibited improvement in BCVA, but no statistically significant difference between the groups existed at month 24 [17]. Other secondary outcomes, such as cystoid macular edema, rate of systemic adverse events, and even quality of life, did not reach statistical significance when compared between the implant and systemic therapy groups [17]. Long-term follow-up of these patients is ongoing.

The fluocinolone acetonide implant, Retisert received Orphan Drug designation from the FDA for chronic, noninfectious, posterior segment uveitis in July of 2000; it was approved for this indication on April 11, 2005, according to FDA documentation, becoming the first intravitreal implant of its kind to do so [18]. Given its success, a newer application has been devised and applied for DME. The Iluvien® implant also utilizes the CS fluocinolone acetonide, but the improved, minute intravitreal insert affords the ophthalmologist the flexibility of out-patient/in-office administration [19]. Phase III follow-up trials using this less invasive long-acting device are currently underway in DME, and very recently, have started seeking patients with uveitis [19].

Drug delivery devices hold exciting promise in the future care of uveitis patients. They can be minimally invasive, with the shift in administration setting from required operating room time to in-office placement. The side effect profile is relatively low, compared with some secondary to systemic therapies. These devices can be sight-saving for patients unable to sustain immunomodulatory treatment.

■ Iontophoresis

To the medical community, iontophoresis is not a new delivery method for medication. To ophthalmology, the process of charging drug particles with minute current to drive them into the eye, is relatively novel, and is proving to be formidable in treating ocular inflammation. Similar to the drug-eluting devices, iontophoretic CS delivery affords the patient effective elimination of inflammation without the systemic side effects associated with CS use; an additional benefit to treatment is the fact that it is less invasive than implant devices and does not require minor surgery [20]. The drug of choice, typically a potent CS (as this method has been adapted in antibiotics, antivirals, NSAIDs and others), is loaded onto a drug-saturated device connected to electrical current [20]. This donor electrode fits snugly onto the external eye, and with the loaded drug, serves as the conductor of the delivered current. A return electrode is placed on the patient near the eye (the forehead), as a hand-held generator delivers treatment via electrophoresis, electroosmosis and electroporation [20]. It is postulated that this method of delivery affords enhanced movement and increased transport of the drug, given its new charge, and alteration of the tissue barrier, increasing the inherent membrane permeability [20].

To date, several clinical trials have been conducted in an effort to examine the safety and efficacy of this treatment for uveitis [20–22]. In the early stages of development, methylprednisolone was shown to be safe, well-tolerated, easily applied, and effective in reducing severe ocular inflammation in 18 patients experiencing corneal graft rejection; 80% of the eyes showed a “complete reversal of the rejection process, with no significant side effects” [20,23,24]. Recently, the results from a Phase I/II clinical study that included 42 patients (40 eyes) were published [21]. Conducted at multiple sites, this double-masked, randomized, parallel dose comparison study aimed to evaluate the effectiveness of EGP-437 (40 mg/ml dexamethasone phosphate solution) at different iontophoretic and pharmacologic doses, with prednisolone acetate 1% optional rescue, the current standard of care [21]. Patients were randomized to one of four treatment arms: 1.6 mA-min at 0.4 mA, 4.8 mA-min at 1.2 mA, 10.0 mA-min at 2.5 mA, or 4.0 mA-min at 3.5 mA; all treatment durations were set to 4 min [21]. Inclusion criteria consisted of diagnosed noninfectious anterior uveitis, having a score of 1.5+ ACCs or greater; patients were excluded if the cause of their uveitis was infectious, if they had a reported history of glaucoma, or they had used topical CSs 48 h prior to study drug administration [21]. After a single treatment given on day 0, 22 patients (55%) reported an ACC score of

0 at day 14 (not dose dependent) [21]. By day 28, 32 out of 40 patients (80%) had achieved a score of 0, although eight required rescue therapy [21]. Researchers concluded that the lowest iontophoretic dose level afforded the greatest clinical benefit to patients, based on ACC scores temporally and requirements for rescue [21]. Commonly reported side effects according to this study included: conjunctival hyperemia (n = 21), punctate keratitis (n = 15), conjunctival edema (n = 13), eyelid edema (n = 8) and eye pain (n = 8) [21]. Transient changes in IOP and BCVA were also mentioned, but were mild and transient [21]. Despite the impressive outcome, this study had no control group, greatly weakening the strength of the reported results.

The largest clinical trial to date, a randomized, double-masked comparative Phase III clinical trial, compared EGP-437 iontophoretic treatment (at 4.0 mA-min at 1.5 mA) and placebo topical drops to iontophoresis with sodium citrate buffer and prednisolone acetate 1% topical drops. In this study that spanned 45 clinical sites in the USA, 193 patients were randomly assigned into one of two treatment arms: iontophoretic treatment with EGP-437 on days 0 and 7, or 14 days of daily treatment of prednisolone acetate 1% ophthalmic solution, which was followed by two weeks of standard tapering. The primary efficacy end point in this noninferiority study was set as the proportion of patients with ACC count of zero on day 14, defined as a complete response. In all randomized subjects by day 14, two iontophoretic treatments with EGP-437 resulted in 32 complete responses out of 96 patients; topical prednisolone acetate 1% ophthalmic suspension also produced 32 complete responses out of 97 patients. Regarding safety, the incidence and severity of treatment-emergent adverse events in both groups were comparable, and there were fewer incidences of elevated IOP in the EGP-437 group [PATANE M, UNPUBLISHED DATA].

To summarize, iontophoresis of CS may be a safe and effective method for inflammation control. It is easily delivered in the office, rapid and avoids a host of systemic side effects associated with other delivery forms of CS.

Novel calcineurin inhibitors

T-cell inhibition is the primary method by which cyclosporin, tacrolimus, sirolimus and everolimus are thought to exert action [1]. Although not completely understood, calcineurin inhibitors essentially disrupt signal transmission necessary for activation of certain T lymphocytes through competitive binding at the transcriptional activator site of IL-2 [1]. These compounds appear to be superior for immune suppression

because T suppressor cells remain relatively unaffected [1]. Adapted for use in uveitis, their other clinical uses include psoriasis, rheumatoid arthritis and organ rejection prevention.

Sirolimus, a T-cell inhibitor of the mTOR pathway adapted from the organ transplantation arena, has been examined for safety and efficacy in extinguishing ocular inflammation, both orally and locally. An initial pilot study evaluated oral sirolimus in eight patients with severe noninfectious posterior uveitis; five achieved positive uveitic outcomes (symptom improvement and/or regression of vasculitis) with decreased or discontinuation of concomitant CSs [25,26]. A similar-sized pilot study followed, analyzing subconjunctival administration of sirolimus in chronic, active anterior uveitis ($n = 5$) [27]. A single dose of 30 μ l of sirolimus was injected into the study eye of patients experiencing $\geq 1+$ ACCs despite topical CS administration [27]. After a follow-up period of 16 weeks showed all enrolled patients achieved a score of 0 ACCs at some point in the study (that is, all patients exhibited improvement postinjection); two out of five patients were graded as 0.5+ ACCs after achieving a score of zero at the immediately previous follow-up visit [27]. All patients were able to decrease or discontinue their baseline CS use, and reported adverse events were mild and transient [27]. A larger, prospective, open-label trial followed: 30 patients with both active and inactive posterior, intermediate and pan-uveitis were enrolled in the study [28]. Fifty percent of the patients received sirolimus subconjunctivally, and 50% received the medication intravitreally; 66 and 62 injections were administered in each group over a period of 6 months, respectively [28]. Overall, approximately 40% of the patients treated exhibited a complete response to sirolimus treatment [28]. Improvements in visual acuity, inflammation status, central macular thickness and quality of life were reported [28]. Patients who presented with inflammation ($n = 20$) showed a statistically significant reduction in vitreous haze at months 3 and 6 [28]. Of the patients who were not receiving any treatment at study onset, 71% exhibited an impressive ≥ 2 step vitreous haze reduction [28]. Conversely, of the patients who were on treatment (namely, CSs), 100% ($n = 13$) were able to taper or discontinue daily dosages of CS therapy [28]. Approximately 88% of those with inactive inflammation at the onset of the trial maintained uveitic quiescence at month 6 [28]. Principal side effects reported for this pharmacologic include inflammation at the injection site and possible progression of cataract, though further research on this frontier is necessary [27,28]. A follow-up study exploring appropriate dose and timeline is currently ongoing, in addition to

the first, official Phase III, multicenter, randomized, double-masked trial assessing safety and efficacy of intravitreal sirolimus in posterior uveitis.

Everolimus approved for use in various cancers and in the prevention of kidney transplantation rejection, may be another viable therapy for the treatment of uveitis. The initial open-label pilot study, conducted in Germany, sought to investigate the efficacy of everolimus in refractory anterior and posterior uveitis patients [29]. Twelve patients, who failed to adequately respond to cyclosporine A therapy and with active disease, were assessed primarily for uveitis inactivity, and secondarily, for complications and the steroid-sparing effect of everolimus [29]. All 12 patients achieved disease inactivity, defined as $<0.5+$ ACC and the absence of chorioretinal lesions within 3 months, after presentation with bilateral disease [29]. Disease inactivity was maintained in six out of 11 patients who reached the 12-month study completion [29]. Four patients were able to completely discontinue systemic CS therapy, and four additional patients were able to taper doses of systemic CS under 10 mg per day, with the use of everolimus [29]. Headache and abdominal pain were subjectively reported, in addition to arterial hypertension development and increasing creatinine levels common with this class of pharmacologic [29].

■ Voclosporin

A close relative of cyclosporin has completed its second placebo-controlled randomized, controlled trial in the FDA approval process [101]. News reports released in late 2012 and early 2013 reported that the large "Phase III clinical study using voclosporin for the treatment of noninfectious uveitis, conducted by Lux Biosciences, Inc. did not meet its primary end point of change from baseline in vitreous haze at 12 weeks or at the time of treatment failure, if earlier"; the pharmaceutical corporation responsible for drug development does not propose to move forward with regulatory submission in this indication [102]. This is a blow to researchers, considering three earlier trials conducted exhibited more promising results. The randomized, double-blinded, placebo-controlled trials aimed to evaluate the effectiveness of voclosporin in active posterior-, intermediate- or pan-uveitis, quiet posterior-, intermediate- or pan-uveitis, and active anterior uveitis, respectively [30]. Poised to become the first CS-sparing therapy approved for use in uveitis, investigators were encouraged by observed inflammation reduction in the posterior uveitides, and strong evidence of CS-sparing success [30,31]. In all three trials, 96–98% of patients lowered their oral prednisone dose [31]. Significant side effects plagued some patients: deterioration of renal function and

hypertension, specifically [31]. A final trial was conducted, and the preliminary results released revealed an inadequate therapeutic effect.

The exploration of the future use of calcineurin inhibitors in the treatment of uveitis is presently ongoing, as this route of immunomodulation is appealing, but not yet perfected. Final results of recently completed clinical trials may spur their development, and future use.

Adapted biologic response modifiers

With highly specific targets and the prospect of avoidance of unpleasant systemic side effects, biologic response modifiers afford the ocular immunologist an additional line of adapted medications for use in patients with a recalcitrant clinical course of uveitis. Popular targets of development are shared among other autoimmune disease entities; commonly, Crohn's disease and Colitis; psoriasis; ankylosing spondylitis; and the psoriatic, rheumatoid and juvenile idiopathic forms of arthritis [1]. Other non-conventional therapies are also gaining popularity. Smaller investigator-initiated trials continue to dominate research findings, as large, prospective trials in uveitis have not yet been completed and/or reported.

■ Anti-TNF- α agents

One specific target in combating autoimmune disorders is deactivation of TNF- α , a cytokine associated with initiation of the immune response via activation of endothelial cells [1]. Curtailing the initiating response to inflammation is an excellent way to achieve inflammatory control. Adalimumab and infliximab have been approved for use in rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, moderate-to-severe chronic psoriasis, ulcerative colitis and Crohn's disease; although not approved for use in uveitis, they have been shown effective against severe cases, and have been used clinically for years. Clinical trials in adalimumab for the indication of active and inactive posterior-, intermediate-, and pan-uveitis are currently underway, while only smaller case studies in infliximab have been completed. Their success has paved the way for similar agents currently forthcoming.

Similar to adalimumab, golimumab is a novel fully humanized anti-TNF- α monoclonal antibody showing promise in matriculating studies in patients with uveitis. The first two documented cases of use were reported by investigators in 2011 [32]. Positive outcomes were seen after 6 or more months of follow-up, despite particularly difficult clinical uveitis histories in both patients [32]. An additional case study in patients with juvenile idiopathic arthritis-associated

recalcitrant uveitis has also been published; this analysis includes three cases [33]. Results support positive initial responses to the therapy, with one patient failing to maintain remission after 6 months of therapy. Interestingly, the two remaining patients achieved complete control of inflammation, both ocular and joint, and "were able to undergo cataract surgery with continued control of inflammation and improvement in visual acuity" [33]. A separate report further confirmed these results in a single patient with refractory Behçet's-associated uveitis [34]. Subcutaneous golimumab helped achieve remission in this patient, according to investigators; additionally, CSs were largely tapered and all systemic disease quiescent during a 6 month follow-up [34]. Although the number of cases overall is small, further research on this therapy is merited. A large-scale clinical trial assessing the incidence of extra-articular manifestations in participants with ankylosing spondylitis treated with golimumab is currently underway; the incidence rate of uveitis attacks before treatment and after the start of treatment serves as the primary outcome measure [103].

Additionally, researchers are developing TNF- α inhibitors to be administered outside of the traditional subcutaneous and intravenous routes. Apremilast, taken orally, and ESBA-105, applied topically, are both provoking efficacy study in other autoimmune etiologies, such as psoriasis, rheumatoid arthritis and diabetic retinopathy; two randomized, controlled trials in patients with uveitis are currently ongoing or have recently completed, one for each compound [25,103]. Positive patient outcomes, as explained above, may merit further research exploiting this pathway in patients suffering from ocular inflammatory disease.

■ Anti-ILs

IL-1, a pyrogenic facilitator of innate immune response, is a focal target for immunomodulation, possibly due to its role in T-cell proliferation [35]. Anakinra, an antagonist to the IL-1 receptor, was first reported effective in a single case of severe, recalcitrant Behçet's disease-associated uveitis [36]. Resistant to or unable to sustain several conventional therapies, the patient's disease course positively responded to daily subcutaneous administration of the antibody within 7 to 10 days [36]. A multicenter, randomized, double-blind, placebo-controlled trial in patients with juvenile idiopathic arthritis followed; 24 patients were enrolled and randomized in a 1:1 ratio [37]. The primary outcome of anakinra efficacy was assessed by a unique cumulative rheumatologic score out of 30, encompassing a global evaluation of disease [37]. Eight out of 12 (67%) patients receiving anakinra treatment were deemed 'responders', as compared with

one out of 12 randomized to the placebo group [37]. Adverse events reported included serious infection, nonserious infection, vomiting, abdominal pain, pain at the injection site, skin lesions and one vertebral collapse [37]. Although active uveitis was not present in all patients enrolled in the study, the results, which indicate a positive response in terms of inflammation management and anakinra's CS-sparing property (six out of 16 patients discontinued CS therapy by the final study visit), may indicate a future place in uveitis treatment for IL-1 antagonists [37]. Currently, clinical trials are ongoing in Behçet's disease, juvenile idiopathic arthritis and posterior blepharitis [103].

Rilonacept, employing a strikingly similar technique as anakinra's anti-IL-1 receptor tactic, is currently undergoing proof-of-concept clinical trials in noninfectious, posterior, intermediate- and pan-uveitis [38].

At the time of this publication, one trial utilizing gevokizumab, an IL-1 β -regulating monoclonal antibody, in the treatment of posterior uveitis had been completed [39]. Seven patients with Behçet's disease were enrolled, and subsequently dosed via single intravenous infusion at 0.3 mg/kg [39]. All enrolled patients saw initial resolution of inflammation within the first week following biologic infusion, and complete resolution by day 21 following the infusion; this was reliant upon the ACC and flare grading, the amount of vitreous haze, and the presence of retinal infiltrates [39]. Impressively, one patient with a hypopyon exhibited nearly-complete resolution by day 1 following the infusion [39]. Five out of seven patients showed an increase in visual acuity, and four patients showed a marked improvement in fluorescein angiography findings [39]. As the trial was preliminary, data on adverse events and long-term follow-up were absent. A large-scale, randomized, double-masked, placebo-controlled study examining safety and efficacy of subcutaneous gevokizumab in the treatment of both active and inactive noninfectious intermediate-, posterior-, or pan-uveitis is currently underway.

Canakinumab, another monoclonal antibody targeting IL-1 β , has sparked interest among uveitis community members. One recently published case report cited remission achievement shortly after subcutaneous administration in a patient with Blau syndrome and a recalcitrant history of related uveitis [40]. The case study reported that after treatment with canakinumab, the patient was able to discontinue CS pulse treatment [40]. Another case study reported inflammation resolution in a patient with Behçet's disease-associated uveitis dosed with intravenous canakinumab; this patient was also refractory to many previous therapies [41]. In 8 weeks of follow-up,

the patient was maintaining remission [41]. No larger clinical trials involving canakinumab and uveitis have taken place to date; however, studies of canakinumab use in juvenile idiopathic arthritis (and its ocular manifestations) are currently ongoing.

Tocilizumab, anti-IL-6, is another anti-interleukin showing promise in treating uveitis. Two separate case reports tout its promise for inclusion in the arsenal against Behçet's disease-associated uveitis [42,43]. Both cases featured recalcitrant clinical courses, in terms of uveitis among other systemic problems; both cases featured significant attenuation of symptoms, and improvement in visual acuity [42,43]. Additionally, both cases reported decreased or complete discontinuation of concomitant systemic CS therapy once remission with tocilizumab was gained; together, this may suggest further application in recalcitrant uveitis [42,43]. Three additional small case reports show tocilizumab may be a viable option for patients failing to achieve remission with TNF antagonists specifically [44–46]. In the first case series, three adult patients with juvenile idiopathic arthritis were treated with intravenous tocilizumab after failing to adequately respond to both etanercept and adalimumab [44]. Two out of three patients exhibited extinguished ocular inflammation and improved visual acuity after receiving tocilizumab therapy [44]. Another case, involving a patient with multiple autoimmune-associated pathologies, showed rapid improvement after one year of tocilizumab infusion treatment: decreased vascular leakage upon fluorescein angiography, fewer large cells in the anterior chamber, and general marked improvement [46]. Three randomized, controlled trials testing the safety and efficacy of tocilizumab in patients with posterior segment uveitis, juvenile idiopathic arthritis-associated uveitis and Behçet's disease are currently underway [103].

Secukinumab, a monoclonal antibody directed against interleukin-17, was initially tested in 60 patients with various autoimmune disorders; 16 of these patients had uveitis [47]. In a set of three placebo-controlled trials, patients with active inflammation due to psoriasis, rheumatoid arthritis and uveitis were appropriately evaluated after single or multiple infusions of experimental medication [47]. Patients enrolled ran the gamut in terms of forms of uveitis; anterior through posterior, and various systemic disease-associated uveitic entities were all represented [47]. Active ocular inflammation was classified by either ACC scores of at least 1+ for anterior segment disease, or a vitreous haze score of at least 1+ for posterior segment disease [47]. Out of 16 patients, 13 showed a one-step or greater improvement in ocular inflammation status by the 8-week timepoint; only

one patient studied exhibited a worsening of uveitis [47]. Researchers went on to classify half of the patients as 'rapid responders', explaining that inflammation resolution (that is, an anterior chamber score of zero, and a vitreous haze score of trace or less) occurred within 14 days of administration [47]. Overall, initial reports of secukinumab assure improvement in visual acuity, a reduction in ocular inflammation, or the ability to decrease and/or stop CS therapy [47]. The side-effect profile compiled based on these trials includes headache, upper abdominal pain, and conjunctival hyperemia; none were deemed serious [47]. Owing to positive initial outcomes, three additional trials were constructed assessing the safety and efficacy of different dosage protocols of secukinumab [48]. Approximately 274 patients were randomized to one of three double-blinded, placebo-controlled studies: secukinumab as adjuvant therapy in Behçet's uveitis; secukinumab versus placebo in active posterior, intermediate or panuveitis; and secukinumab versus placebo in quiescent posterior, intermediate or panuveitis [48]. Active Behçet's disease was determined by incidence of exacerbations within 6 months (must be ≥ 2) [48]. Active uveitis was indicated if the vitreous haze score in at least one eye was $\geq 2+$; inactive disease was characterized by $< 1+$ ACC grading and $< 1+$ vitreous haze for at least 6 weeks [48]. In the initial Behçet's trial, rate of ocular inflammatory recurrence, BCVA, and decrease in vitreous haze did not statistically differ from the placebo group [48]. Due to the poor therapeutic outcome in Behçet's disease patients, the other studies were terminated by the sponsor [48]. Participants enrolled with active and inactive uveitis similarly exhibited no statistically significant differences between the experimental and placebo groups in terms of time to first recurrence, vitreous haze score, or BCVA [48]. A greater number of adverse events were reported in patients treated with secukinumab, as compared with patients randomized to the placebo group [48]. Researchers concluded that poor study design lead to poor results, but the treatment may still hold promise due to its beneficial effect seen when tapering IMT, paired with a favorable safety profile [48]. Six additional cohorts of testing have nearly completed, evaluating the efficacy and safety of secukinumab. The therapy is also currently undergoing trials in other autoimmune diseases.

Anti-ILs, in total, offer moderate-to-high response rates, paired with low side-effect profiles. They are expensive, however, and may be inappropriate for use in specific instances, such as tuberculosis and malignancy. Supporting immunology research to determine the specific roles played in uveitis may guide future R&D, and lead to better patient outcomes.

■ Other immune-mediated complexes & other therapies

Rituximab, a chimeric monoclonal antibody directed against CD20, has shown initial positive outcomes in treating patients with aggressive uveitis. Initially approved for use in types of lymphoma, the intravenous therapy has been reported successful against refractory anterior uveitis, retinal vasculitis secondary to Behçet's disease and juvenile idiopathic arthritis [49–53]. One case of treatment in a patient with Behçet's disease cited rituximab as potentially CS-sparing, reporting the recalcitrant case relented as soon as 6 weeks post-infusion and chronic prednisone was able to be tapered [50]. A pilot study involving 20 patients with Behçet's disease-associated uveitis followed; patients were randomized to receive rituximab or cytotoxic combination chemotherapy and CS [53]. At the 6-month timepoint, the experimental group receiving rituximab exhibited a statistically significant improvement in preset inflammatory measures over the experimental group receiving cytotoxic agents [53]. Adverse events reported from both groups included conjunctivitis, pneumonia, herpes zoster, and infusion-related side effects [53]. All patients receiving rituximab experienced recurrence, but researchers hypothesized after the fact that the dosing protocol may have been to blame [53]. In another patient, intraocular inflammation and cystoid macular edema secondary to uveitis was reported to have improved post-treatment [49,51]. Finally, two case series, with eight and ten patients with juvenile idiopathic arthritis-associated uveitis respectively, commented on successful treatment with rituximab [51,52]. In both trials, all patients had previously failed one or more anti-TNF- α agents; many were CS-dependent [51,52]. After an average of 11–14 months, seven out of eight patients and seven out of ten patients exhibited uveitis inactivity [51,52]. Four out of six patients and seven out of ten patients were able to taper and/or completely discontinue CS therapy with the use of rituximab [51,52]. The latter study also reported a positive clinical effect on patients with concomitant arthritic inflammation [52]. These initial results show a potential future for rituximab in the treatment of uveitis.

Almetuzumab, an anti-CD52 antibody CAMPATH-1H, has been tested in 18 patients with Behçet's disease-associated uveitis in the UK [54]. A total of 15 out of 18 patients exhibited a clinically beneficial response to one course of CAMPATH-1H, while two patients worsened, requiring increased systemic CS use [54]. By month 6, 72% were reportedly in disease remission [54]. Adverse events reported immediately after treatment included fever, chills, backache, wheezing, malaise and

hypothyroidism [54]. These initial results merit further study of this compound.

Abatacept, an antagonist to the CD-80 and CD-86 immune mediators, is showing promise against stubborn cases of juvenile idiopathic arthritis-associated uveitis; to date, four small case series highlighting its success have been published [55–58]. The first revealed a difficult disease course, intolerance to numerous medications, CS dependence and persistent, aggressive disease [55]. Intravenous abatacept once monthly for 18 months resulted in rapid diminution of ocular inflammation and reduction and/or discontinuation of concomitant medications, including systemic prednisone [55]. No adverse events or disease recurrence were reported [8]. Seven patients with juvenile idiopathic arthritis were chronicled in the second study; all had failed infliximab and/or adalimumab prior to undergoing abatacept therapy [56]. All seven patients responded to the therapy; the frequency of uveitis flares decreased from an average of 3.7 episodes in the 6 months prior to therapy, to an average of 0.7 episodes (range 0–2) in the 6 months following therapy administration. Additionally, all patients exhibited improvement in ACC grading. Only one patient was cited to have achieved complete remission. Adverse events reported (all in only one patient) included skin reactions, oral mycosis and arthritis flare [56]. A written response, in the form of a Letter to the Editor from Elhai and associates, to this clinical report revealed two additional cases of juvenile idiopathic arthritis-associated uveitis and abatacept therapy success after TNF- α intolerance and a longer follow-up time [57]. After up to 16 months of observation, both of these patients were free of ocular inflammation. No adverse events were reported, but concomitant medications were unable to be reduced. Given this new data, Zulian and associates responded with an update on the clinical status of their patients; five out of seven are maintaining good control of their uveitis and arthritis after 21 months of follow up and two have discontinued CS use [56]. One patient exhibited a severe relapse, and required increased prednisone and methotrexate therapy [57]. The last small series on abatacept use similarly showed two patients with juvenile idiopathic arthritis failing to respond to conventional therapy [58]. Although significant ocular inflammation subsided in both cases, joint flares continued in spite of therapy in one patient, and CS-sparing remission was not achieved in either patient [58]. Randomized, controlled trials for abatacept treatment in patients with uveitis and patients with Behçet's disease are currently recruiting in the USA [103].

These other therapies hold great promise for future use in uveitis, especially in severe, stubborn cases where

patients have limited therapeutic options remaining for sight-saving treatment. Larger clinical trials will expand existing data on safety and efficacy, and on the CS-sparing effect of each medication. **Table 1** provides an overview of emerging therapies for the treatment of uveitis.

Ongoing challenges in clinical research: a critical evaluation

The potential medications available for treatment of patients with uveitis have exploded over the past 30 years [25]. Still, patients frequently must switch regimens or dosing protocols, seeking that 'perfect fit'. No single drug exists that is able to induce and maintain remission, without CS use and with little to no side effects in every patient; that is the ideal. Lack of existing data, combined with a lackluster effort on behalf of the pharmaceutical manufacturers, may be contributing to the absence of FDA approval for any IMT for uveitis.

The most obvious challenge currently facing uveitis practitioners is the lack of quality data in the use of these medications specific for the indication of uveitis generated by randomized, controlled trials. Because very few of the pharmacologics discussed above actually hold FDA approval with uveitis as an accepted indication, very few large-scale, prospective studies have been conducted. For example, certolizumab pegol, another TNF- α inhibitor has shown promising results against autoimmunity manifesting as Crohn's disease and rheumatoid arthritis; it has yet to be tested in an individual with uveitis. Uveitis trials rarely blaze the trail to approval from preclinical development; HuMax IL-15, an anti-IL, initiated trials in rheumatoid arthritis, and similarly, ustekinumab, anti-IL 12/23, has been approved for use in plaque psoriasis, (though the National Eye Institute is slated to begin a small pilot study utilizing ustekinumab later this year) [35,103]. Neither has been tested in uveitic patients, but both possess immunologic properties necessary for medical translation and are supported by basic biochemical science, making them good candidates for approval, among countless other emerging monoclonal compounds [38].

Additionally, evaluation of this data may be problematic for the practicing clinician. Deciding which reports are reliable, and how much weight to give each set of results is intimidating. How is the clinician to rapidly sift through a myriad of trials?

Pharmaceutical manufacturers serve as the direct impetus behind drug approval. They have the capacity to mount large, prospective randomized trials, the gold standard of evidence backing or dismissing contenders as therapeutic agents. The skyrocketing cost of bringing a compound from bench to market seems to

Table 1. Overview of emerging therapies for the treatment of uveitis.

Compound	Trade name	Target/mechanism	US FDA approval	Reported adverse events
Corticosteroid therapies				
Difluprednate ophthalmic emulsion	Durezol®	Rapid, effective corneal epithelium penetration	Inflammation and pain associated with ocular surgery; endogenous anterior uveitis	Intraocular pressure increase; cataracts; delayed healing; bacterial, viral and/or fungal infections
Dexamethasone intravitreal implant	Ozurdex®	Biodegradable implantable corticosteroid	Macular edema following branch and/or central retinal vein occlusion; noninfectious uveitis affecting the posterior segment	Endophthalmitis; eye inflammation; retinal detachment; intraocular pressure increase; cataracts; delayed healing; bacterial, viral and/or fungal infections; migration to the anterior chamber; conjunctival hemorrhage
Sustained release fluocinolone acetonide implant	Illuvien®	Biodegradable implantable corticosteroid	Trials underway: diabetic macular edema and chronic noninfectious uveitis affecting the posterior segment	Cataract progression; intraocular pressure increase
Iontophoretic dexamethasone phosphate ophthalmic solution	N/A	Application of small electrical current to increase ion (drug) movement into the eye	Trials recently completed: acute anterior uveitis, non-necrotizing anterior scleritis and dry eye	Transient ocular hyperemia; keratitis; ocular discomfort; conjunctival edema
Novel calcineurin inhibitors				
Sirolimus	Rapamune®	mTOR pathway inhibitor	Prevention of kidney transplant rejection	Hypercholesterolemia; hypertriglyceridemia; thrombocytopenia; hypophosphatemia, hyperkalemia; peripheral edema and weight gain; upper respiratory infection, dyspnea and pharyngitis; anemia; leucopenia, hypertension; diarrhea; arthralgias; fever, rashes, and tremors
Everolimus	Afinitor®, Zortress®	Protein kinase inhibitor	Hormone receptor-positive, HER-2 negative breast cancer; progressive neuroendocrine pancreatic tumors; advanced renal cell carcinoma; renal angiomyolipoma and tuberous sclerosis complex	Noninfectious pneumonitis; infections; oral ulcerations; renal failure; laboratory test alterations; embryo-fetal toxicity; stomatitis
Voclosporin	Voclera, Luveniq®	Transcriptional activation of T cells	Not at this time	Lymphopenia; decreased renal function; hypertension hirsutism; gingival hyperplasia
Adapted biologic response modifiers				
Golimumab	Simponi®	TNF- α inhibitor	Moderate to severely active rheumatoid arthritis; active psoriatic arthritis; active ankylosing spondylitis; moderate-to-severe ulcerative colitis	Serious infections; invasive fungal infections; hepatitis B reactivation; malignancies; heart failure; demyelinating disease; hypersensitivity reactions; upper respiratory tract infections; nasopharyngitis; injection-site reactions
ESBA-105	N/A	TNF- α inhibitor	Trials recently completed: anterior uveitis; cataract; chronic dry eye	N/A
Anakinra	Kineret®	IL-1 receptor antagonist	Active rheumatoid arthritis; cryopyrin-associated periodic syndromes	Neutropenia; injection-site reactions; infections; malignancy; hematologic events; hypersensitivity reactions; immunogenicity; upper respiratory tract infections; headache; diarrhea; sinusitis; arthralgia; flu-like symptoms; abdominal pain

Table 1. Overview of emerging therapies for the treatment of uveitis (cont.).

Compound	Trade name	Target/mechanism	US FDA approval	Reported adverse events
Rilonacept	Arcalyst®	IL-1 antagonist	Cryopyrin-associated periodic syndromes (familial cold autoinflammatory syndrome and Muckle–Wells syndrome)	Serious infections; hypersensitivity reactions; injection-site reactions; upper respiratory tract infections
Gevokizumab	N/A	IL-1-b antagonist	Trials underway/recently completed: active and inactive noninfectious uveitis of the posterior segment; scleritis; acne vulgaris; Type I and II diabetes; pyoderma gangrenosum; erosive osteoarthritis; familial cold autoinflammatory syndrome and Muckle–Wells syndrome	Diarrhea; nasopharyngitis; pharyngitis; acne; cushingoid; upper respiratory tract infection; headache; oral herpes; cough; oropharyngeal pain; glaucoma; nausea; flu-like symptoms; hepatotoxicity; back pain
Canakinumab	Ilaris®	IL-1-b antagonist	Cryopyrin-associated periodic syndromes (familial cold autoinflammatory syndrome and Muckle–Wells syndrome); active systemic juvenile idiopathic arthritis	Serious infections; nasopharyngitis; upper respiratory tract infections; diarrhea; influenza; headache; nausea; abdominal pain; injection-site reactions
Tocilizumab	Actemra®	IL-6 receptor antagonist	Moderate to severely active rheumatoid arthritis; active polyarticular juvenile idiopathic arthritis; active systemic juvenile arthritis	Serious infections; gastrointestinal perforation; changes in neutrophils, platelets, lipids and liver function tests; hypersensitivity reactions; upper respiratory tract infections; nasopharyngitis; headache; hypertension
Secukinumab	N/A	IL-17A antagonist	Trials underway/recently completed: noninfectious uveitis of the posterior segment; moderate-to-severe plaque psoriasis; rheumatoid arthritis	Headache; elevated intraocular pressure; eye pain; blurred vision; dizziness; abdominal pain; fever; joint pain; fatigue; nausea; infection; anaphylaxis
Rituximab	Rituxan®	CD-20 directed cytolytic antibody	Non-Hodgkin's lymphoma; chronic lymphocytic leukemia; rheumatoid arthritis; granulomatosis with polyangiitis (Wegener's)	Infections; cardiac arrhythmias and angina; bowel obstruction and perforation; cytopenia (neutropenia, lymphopenia); infusion reactions; fever; chills; infections; upper respiratory tract infections; nasopharyngitis; urinary tract infection; bronchitis; cardiac events; nausea; diarrhea; headache; muscle spasms; anemia; peripheral edema
Alemtuzumab	Campath-1H, Lemtrada®	CD-52 directed cytolytic antibody	B-cell chronic lymphocytic leukemia	Cytopenia; infections; infusion reactions; cytomegalovirus; nausea; emesis; diarrhea; insomnia
Abatacept	Orencia®	CD-80, CD-86 directed antibody via selective T-cell costimulation inhibition	Rheumatoid arthritis; juvenile idiopathic arthritis	Hypersensitivity and anaphylaxis; infections; headache; upper respiratory tract infections; nasopharyngitis; nausea

serve as a major deterrent in the case of uveitis therapy; patients can be difficult to recruit, and some contention among investigators may exist regarding the clinical risk–benefit profile.

Future perspective

Patients with uveitis need additional therapies: therapies that eliminate inflammation and retain remission; therapies offering high efficacy and low side-effect profiles; and therapies that are considerate of quality of life and/or patient satisfaction and comfort. The progression of uveitic treatment has propelled us from few treatment options with high side-effect profiles, to many treatments options with highly-directed targets and lower side-effect profiles. Despite such rapid advancement, more work still remains. Novel, less invasive treatment methods, such as iontophoresis or topical application (as opposed to transseptal injection), hold promise on the forefront of patient endorsement and approval. Adaptation of therapies once administered intravenously to subcutaneous route is to be further explored, to allow more flexible patient care. Dosing quantity and timeline should be studied, in order to determine the least frequent dosing with highest compliance and lowest side effects experienced. If possible, pharmacogenetic samples should be collected and analyzed, to determine if certain genetic markers augment or detract from a drug's effects. Therapies should be used in adjuvant and studied in an effort to lower the dosage of both therapies, and expectantly, lower the possibility of adverse side effects.

The negative outcomes associated with long-term CS use are well described in the literature and significant progress has been made to date to provide CS-sparing IMT options to patients with autoimmune disease. This pursuit must continue; developing therapies that allow for durable, possibly life-long remission through complete absence of inflammation, concomitant with no systemic, topical, or local CS use.

Clinicians can improve future clinical trials not by increased participant numbers alone, but by focusing studies on specific etiologic-associated uveitic entities, expanding patient and clinician knowledge about specific trends in diseases causing uveitis. Clinical baseline, clinical courses, effective treatment and risk factors associated with relapse may differ among these. Elucidation of different responses to a novel topical CS based upon the patient's lens status, or which serum rheumatologic inflammatory markers can predict recalcitrance of uveitis, is vital information, and serve as examples of how clinicians should design studies. Small pilots may provide initial evidence that adaptation of therapy is possible. However, this presents a difficult and exciting prospect for clinicians; how do we decide, and adequately advise patients, of which novel treatment

will be effective, when the list of available monoclonal antibodies is growing by the day?

The responsibility is not held solely by the investigator; pharmaceutical manufacturers share in this challenge, and should increase clinical testing in uveitis. Further adaptation of pharmacologics used in other autoimmune disease may be the answer, and must rely on the fundamental immunologic evidence. The research and development departments of these corporations have to fill the gaps in basic science where clinicians are unwilling or pragmatically unable. Illuminating specific processes associated with uveitis, down to the smallest details, will provide guidance on which paths pharmacologics should exploit for the best clinical results for these patients. Given the associated costs, pathologies with multiple autoimmune manifestations may be given priority, such as juvenile idiopathic arthritis, or HLA-B27-associated ankylosing spondylitis. Advancements in these diseases benefit both medical fields, ophthalmology and rheumatology, and allow for 'one size fits all' symptom relief, in terms of disease management. Overall, successful FDA approval of these medications may afford pharmaceutical companies and patients bidirectional benefit; pharmaceutical corporations increase capital through an expanded market, and patients experience increased access to effective treatments, which may be currently limited by 'off-label' preauthorization restrictions. Regulatory agencies have a duty to protect patients through trial oversight, but must walk a fine line when it comes to stringency; trial design needs to be more flexible and based on clinical practice. Recommendations pertaining to protocol design, rooted in real-time clinical medicine, must not go unheard. A healthy, symbiotic relationship between sponsors, regulatory agencies and providers must be maintained if drug approval is to occur in a reasonable time frame and at an appropriate cost.

The need for effective therapies is real and dire. Patients with uveitis are dependent upon valuable techniques and treatments to preserve their vision. Modern medicine has come very far, but a long road still lies ahead.

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Executive summary

Background

- Uveitis is a potentially sight-robbing disease. Worldwide, the burden of disease is significant. Although historically practiced, chronic or repeated corticosteroid monotherapy is an unacceptable treatment option for patients with uveitis. Treatment aimed at extinguishing inflammation and preventing recurrence can and should be achieved through limited use of corticosteroids and immunomodulatory therapy. Few newer treatments in uveitis are explicitly approved for use in uveitis, but many are adapted after approval in other autoimmune indications and exhibit positive outcomes reported in case series.

Recent advances in corticosteroid therapy

- More potent topical corticosteroids, and newer methods of delivery of corticosteroids currently comprise the field of available, approved pharmacologics. Collectively, these medications afford higher patient compliance through less frequent dosing, or the complete absence of dosing.

Novel calcineurin inhibitors

- This class of medications may provide a viable route for uveitis specialists to target in battling ocular inflammation; trials are underway in several different compounds from this class of pharmacologic.

Adapted biologic response modifiers

- High specificity is thought to translate to more efficacious outcomes and fewer side effects with administration. This class of medications has extensive reach, and is growing daily. While no medications are currently approved for use in uveitis, many trials are underway and approval in one or more may be on the horizon.

Ongoing challenges in clinical research; a critical evaluation

- Many challenges befall the practicing uveitis specialist in regards to clinical research and treatment. The number of available treatments for uveitis has grown significantly in the past few decades, but still very few are approved for on-label use. Quality data from prospective, randomized, controlled trials are virtually nonexistent in many available medications.

Future perspective

- The future of uveitis therapy relies on results from properly designed, large, randomized-controlled trials of immunomodulatory therapy, several of which are ongoing. Effective therapies with a low side-effect profile and corticosteroid-sparing ability are highly desired, and necessary to preserve vision in patients with ocular inflammatory disease.

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