Future Therapies for Chronic Noninfectious Uveitis

New drugs and innovative drug delivery systems will pave the way for future treatments in uveitis.

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Local and systemic corticosteroids constitute first-line therapy for virtually all patients with noninfectious uveitis.[1] Prolonged corticosteroid use can produce toxic effects, however, and so corticosteroid-sparing immunomodulatory therapies (IMTs) have assumed an increasingly important role in the management of chronic ocular inflammation.[2,3] The more commonly used non-corticosteroid immunosuppressive agents include antimetabolites, such as mycophenoloate mofetil, methotrexate, and azathioprine; leukocyte signaling inhibitors, such as cyclosporine and tacrolimus; tumor necrosis factor (TNF)-α inhibitors, such as infliximab (Remicade, Janssen), adalimumab (Humira, Abbott Laboratories), and golimumab (Simponi, Janssen); and the alkylating agents cyclophosphamide and chlorambucil, which are reserved for the most severe vision- or life-threatening conditions.[2,4] These and other currently available agents are summarized in Table 1.

Each of the currently available treatments for chronic noninfectious uveitis has its own issues, however.[3,4] All have drug-associated toxicities and, even in quite experienced hands, limited efficacy in 30-40% of patients. Fortunately, no fewer than 12 therapies are now in clinical development for chronic noninfectious uveitis (Table 2). These therapies represent both novel agents and established drugs utilizing innovative drug delivery systems. This review provides a summary of these emerging treatments for uveitis. All of these agents were identified through a search of http://www.clinicaltrials.gov and Pubmed at http://www.ncbi.nlm.nih.gov/pubmed.

No fewer than 12 therapies are now in clinical development for chronic noninfectious uveitis. These therapies represent both novel agents and established drugs.

THERAPIES IN LATE-STAGE DEVELOPMENT (PHASE 3)

DE-109 (Santen Pharmaceutical Co.): DE-109 is a novel intravitreal formulation of the immunosuppressant sirolimus, which blocks leukocyte activation and the production of inflammatory cytokines (including IL-2, IL-4, and IL-5) by inhibiting mammalian target of rapamycin (mTOR). DE-109 has been administered both subconjunctivally and intravitreally in clinical studies.[5,6] When given intravitreally, DE-109 forms a slowly dissolving depot in the vitreous humor. This limits the immunosuppressive effects of DE-109 to the eye, thereby minimizing systemic exposure.[7]

DE-109 has been studied in conditions including dry eye syndrome, age-related macular degeneration, and diabetic macular edema (DME). In a phase 1 trial involving 50 DME patients, no dose-limiting toxicities were seen with intravitreal doses as high as 352 µg and subconjunctival doses as high as 1760 µg.[5] The most common adverse event was mild conjunctival hemorrhage, in 80% of patients. Early studies involving a limited number of patients with chronic noninfectious uveitis have suggested that sirolimus and DE-109 may improve signs and symptoms related to intraocular inflammation and reduce the burden associated

TABLE 1. COMMONLY USED TREATMENTS FOR PATIENTS WITH NONINFECTIOUS INTERMEDIATE, POSTERIOR, AND PANUVEITIS

Drug	Mechanism of action	Route of administration and dose	FDA approved indications	Clinical development for NIU	Manufacturer
Drugs used on-label for chronic NIU					
Transcription factor inhibitors: Corticosteroids					
Prednisone (or bioequivalent corticosteroid)	Glucocorticoid receptor agonist	Oral/IV; 0.5-1.5 mg/kg/day	Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa		Multiple/ generic
Triamcinolone acetonide	Glucocorticoid receptor agonist	IVT injection; 20-40 mg/ 0.05-0.1 mL	Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammation unresponsive to topical corticosteroids		Alcon
Fluocinolone acetonide intravitreal implant	Glucocorticoid receptor agonist	IVT implant; 0.59 mg	Chronic NIU affecting the posterior segment of the eye		Bausch & Lomb
Dexamethasone intravitreal implant	Glucocorticoid receptor agonist	IVT implant; 0.7 mg	NIU affecting the posterior segment of the eye		Allergan
Drugs used off-label for chronic NIU					
Transcription factor inhibitors: non-corticosteroid immunosuppressive agents					
Cyclosporine A	Calcineurin inhibitor	IV or oral; Sandimmune: 2-5 mg/kg/day; Neoral: 2.5-4.0 mg/kg/day	RA Psoriasis	Phase 3: Behçet's disease	Multiple/ generic
Tacrolimus/ tacrolimus prolonged release	Calcineurin inhibitor	Oral; 0.15-0.3 mg/kg/day	Transplant rejection		Astellas
Sirolimus/ rapamycin	mTOR inhibitor	Oral; 2 mg/day	Transplant rejection; prevention of restenosis		Pfizer
Antimetabolites					
Azathioprine	Inhibits nucleic acid synthesis	Oral; 50-150 mg/day	RA		Multiple/ generic
Leflunomide	Inhibits nucleic acid synthesis	Oral; 20 mg/day	RA		Multiple/ generic
Methotrexate	Inhibits nucleic acid synthesis	Oral; 10-20 mg/wk	RA Psoriasis Polyarticular-course juvenile RA	Phase 4: sarcoid-associated uveitis; phase 3: First-line NIU; phase 1/2: intermediate NIU by IVT	Multiple/ generic
Mycophenolate mofetil	Inhibits nucleic acid synthesis	Oral; 1000-2000 mg/day	Transplant rejection	Phase 3: 1st-line NIU	Multiple/ generic

TABLE 1. COMMONLY USED TREATMENTS FOR PATIENTS WITH NONINFECTIOUS INTERMEDIATE, POSTERIOR, AND PANUVEITIS (CONTINUED)

Drug	Mechanism of action	Route of administration and dose	FDA approved indications	Clinical development for NIU	Manufacturer
Mycophenolate sodium (enteric coted)	Inhibits nucleic acid synthesis	Oral; 720 mg bid	Transplant rejection	Phase 3: Intermediate NIU	Novartis
Biologics					
Adalimumab	TNF inhibitor	SC; 40-80 mg every 2 wks (adults)	RA PsA AS Crohn's Psoriasis Pediatric polyarticular JIA	Phase 3: Active and inactive posterior segment NIU and Behçet's; phase 1: any NIU (IVT injection)	Abbott
Infliximab	TNF inhibitor	IV; 3-10 mg/kg every 4-8 wks	Adult UC/Crohn's Pediatric UC/Crohn's RA AS PsA	Phase 3: Behçet's disease	Janssen (US)/ Mitsubishi Tanabe (Japan)
Etanercept	TNF inhibitor	SC; 25 mg 2-3 times per wk	RA PsA AS Psoriasis Pediatric polyarticular JIA		Pfizer
Golimumab	TNF inhibitor	SC; 50 mg monthly	RA PsA AS		Janssen
IFN-α2A	Immunomodulator	SC; 6 × 106 IU/day	Hepatitis C infection	Phase 3: Behçet's disease	Multiple/ generic
IFN-γ1b (Actimmune)	Immunomodulator	SC; 1×106 IU/m^2 body area (1.5 µg/kg/dose if whole body surface area ≤0.5 m^2) 3 times/wk	Chronic granulomatous disease	Phase 1/2: anterior uveitis & uveitic ME (topical)	InterMune
Alkylating agents					
Cyclophosphamide	Crosslinked DNA	Oral; 2-3 mg/kg/day	Lymphoma		Multiple/ generic
Chlorambucil	Crosslinked DNA	Oral; 0.1-0.2 mg/kg/day	Chronic lymphocytic leukemia		BMS

AS = ankylosing spondylitis; BMS = Bristol Myers Squibb; CS = corticosteroid; FDA = US Food and Drug Administration; IFN-α = Interferon-alpha; IFN-γ = Interferon-gamma; IV = intravenous; IVT = intravitreal; JIA = juvenile idiopathic arthritis; ME = macular edema; mTOR mammalian target of rapamycin; NIU = noninfectious uveitis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SC = subcutaneous; TNF = tumor necrosis factor.

with steroids and systemic immunosuppression.[6,8] In a phase 2 study of 30 patients with noninfectious uveitis who were given subconjunctival or intravitreal injections of sirolimus on days 0, 60 and 120, visual acuity improved after 6 months in 39% of patients and stabilized in another 39%, while vitreous haze improved in 82%. Moreover, all 20 patients receiving corticosteroid therapy at the beginning of the study were able to have their doses decreased at 6 months. Of reported serious adverse events, none were judged to be the result of DE-109 administration.[8]

DE-109 is currently being evaluated in a randomized, double-masked, multinational phase 3 trial in patients with active noninfectious uveitis. Enrollment is under way. An estimated 500 patients will be randomized to DE-109 intravitreal doses of 44 µg, 440 µg, or 880 µg every 2 months. The primary end point is the percentage of patients with a vitreous haze score of 0 at month 5. Secondary end points include the percentage of patients on ≤5 mg/day of prednisone at this time point.[9]

Adalimumab (Abbott Laboratories): The TNFα inhibitors have significantly altered the treatment landscape for systemic autoimmune diseases over the past two decades, and have been increasingly used off-label in the management of refractory uveitis. Three of these agents—infliximab, adalimumab, and etanercept—have been used to treat a range of uveitic disorders, with particularly promising results seen in Behçet disease and juvenile idiopathic arthritis.[10-13]

Adalimumab a fully humanized, full-length monoclonal antibody given as a subcutaneous (SC) injection every 2 weeks, is currently being evaluated in 2 phase 3 clinical trials of noninfectious posterior-segment uveitis. Visual I in active uveitis and Visual II in inactive uveitis (both N=250)[14,15] are 80-week studies comparing adalimumab, 40 mg SC every other week (after an initial 80 mg loading dose) to a matching placebo with all subjects receiving a standardized prednisone induction and taper schedule. The primary outcome is time to treatment failure, as defined by worsening in retinal lesions, anterior chamber cells (ACC), vitreous haze, or visual acuity. The percentage of patients successfully tapering down to a prednisone dosage of 5 mg/day is a secondary outcome. Both trials are currently recruiting. Patients from both trials will be enrolled in a single long-term (up to 282 weeks) open-label follow-up.

EGP-437 (Eyegate Pharmaceuticals, Inc.): EG)-437 is a dexamethasone phosphate 40 mL solution that is delivered to the eye via iontophoresis, a technique whereby a small electrical field is applied to the ocular surface to effect delivery of charged particles across the ocular surface. Dexamethasone phosphate, a prodrug of dexamethasone, was selected for iontophoresis because it possesses the necessary electrical charge and aqueous solubility at physiologic pH levels. EGP-437 has been evaluated in both phase 2 and phase 3 trials for the treatment of dry eye and although delivery of dexamethasone phosphate via the Eyegate II iontophoresis platform appears to be well tolerated[16] detailed safety and efficacy results from the most recent phase 3 trial have yet to be published.[17]

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The safety and efficacy of dexamethasone phosphate delivered via the Eyegate II iontophoresis platform was evaluated in a phase 1/2 trial in patients with noninfectious anterior uveitis. Subjects were randomized to 1 of 4 iontophoresis dose groups—1.6, 4.8, 10.0, and 14.0 mA-min.[18] The primary endpoint was time to an ACC score of zero. Sixty percent of participants achieved zero anterior chamber cells by day 28.

The 1.6-mA-min dose was found to be most effective, with an ACC score of zero being achieved in this group at a median of 11.5 days, vs 31 days for the 14.0 mA-min group.[18] Based on these findings, a phase 3 trial is currently under way comparing EGP-437 at a dose of 4.0 mA-min with topical 1% prednisolone acetate. This 8-week trial will enroll an estimated 200 patients.[19] The primary outcome measure is the percentage of patients who achieve an ACC count of zero by day 14.

Gevokizumab (XOMA 052; XOMA Corporation): Gevokizumab is a recombinant humanized antibody targeting the proinflammatory cytokine interleukin (IL)-1β. Gevokizumab was initially studied for the treatment of type 2 diabetes, due to the role that IL-1β plays in β-cell failure. Although the phase 2 study in diabetes showed statistically significant and dose-dependent inhibition of C-reactive protein, a validated marker for inflammation, the clinical trial failed to show significant improvement in hemoglobin A1c levels at higher doses and so the program was halted.[20]

A phase 2 proof-of-concept study examined the safety and efficacy of gevokizumab in 7 patients with acute posterior or panuveitis associated with Behçet's disease (monocytes in Behçet's disease patients produce high

TABLE 2. DRUGS CURRENTLY IN DEVELOPMENT FOR THE TREATMENT OF NONINFECTIOUS UVEITIS

Drug*	Mechanism	Target disease	Route of administration	Study location	Sponsor
Phase 3					
DE-109 (sirolimus)	mTOR inhibitor	Posterior-segment NIU	IVT	Global	Santen
Adalimumab	TNF inhibitor	Posterior-segment NIU (active or inactive)	SC	Global	Abbott
EGP-437 (Iontophoretic dexamethasone phosphate)	Glucocorticoid receptor agonist	Anterior-segment NIU	Topical/ iontophoretic	US	Eyegate Pharmaceuticals
Gevokizumab (XOMA 052)	Anti- IL-1β antibody	Posterior-segment NIU (including Behçet's)	SC	Global	XOMA (US/Japan); Servier (All other global regions)
Voclosporin (LX211)	Calcineurin inhibitor	Posterior-segment NIU	Oral	US, Canada, France	Lux Biosciences
Phase 1/2					
ESBA105	TNF inhibitor	Acute anterior uveitis	Topical	Germany	ESBATech AG (Acquired by Alcon)
LFG316	Complement inhibitor (C5)	Active multifocal choroiditis and panuveitis	IVT	US	Novartis
Peptide B27PD†	Tolerance for retinal antigens	Chronic NIU	Oral	US	NEI/ENZO Biochem
Sotrastaurin (AEB071)	PKC Inhibitor	ME-associated posterior segment NIU	Oral	US	Novartis
Ustekinumab	IL-12 inhibitor	Active posterior-segment NIU	SC	US	NEI
Abatacept	CD28 inhibitor	Refractory NIU	IV	US	Oregon Health and Science U/BMS
Tocilizumab	IL-6R inhibitor	Uveitis associated with JIA	IV	US	Oregon Health and Science U/Genentech

*Compounds in development and clinical trial information were identified using http://www.clinicaltrials.gov amd Pubmed at http://www.ncbi.nlm.nih.gov/pubmed.
†Peptide B27PD is a retinal antigen protein fragment.
BMS = Bristol Myers Squibb; IL = interleukin; IV = intravenous; IVT = intravitreal; JIA = juvenile idiopathic arthritis; ME = macular edema; mTOR = mammalian target of rapamycin; NIU = noninfectious uveitis; PKC = protein kinase C; SC = subcutaneous; TNF = tumor necrosis factor.

levels of IL-1β).[21] In all patients, the uveitis was resistant to azathioprine or cyclosporine. An intravenous infusion of gevokizumab, 0.3/mg/kg, led to complete resolution of ocular inflammation in all patients at a median of 14 days, with a median duration of response of 49 days. Five patients received a second intravenous infusion, after which they were attack free for a median of 115 days. IL-1β production was reduced by 97%. There were no treatment-related adverse events.[21] A phase 3 program, expanded to include patients with other forms of noninfectious, nonanterior uveitis, has been initiated for gevokizumab.[22]

Voclosporin (LX211; Lux Biosciences): Voclosporin is an orally active calcineurin phosphatase inhibitor with potent immunosuppressive activity. Voclosporin has been evaluated in a series of phase 2/3 trials that included 558 patients with active or quiescent posterior uveitis or active anterior uveitis. In active posterior disease, voclosporin reduced vitreous haze by 50% and prolonged the time to recurrence by twofold; while in quiescent patients, it reduced the frequency of exacerbations by 50%.[23] Importantly, the reduction of inflammation by voclosporin in active posterior uveitis was observed in important subpopulations of patients including those patients with the highest degree of inflammation; patients for whom systemic corticosteroids were determined to be medically inappropriate by the investigator; and in patients with best corrected visual acuity of less than 20/200 in the study eye. In all 3 studies, 96% to 98% of posterior uveitis patients were able to reduce their oral prednisolone dosage to ≤5 mg/d.[23] In these trials, hypertension (15%), impaired renal function (8%), and hirsutism (5%) were observed. An additional phase 3 safety and efficacy trial is currently ongoing,[24] the results of which are anticipated in the first quarter of 2013.

THERAPIES IN EARLY-STAGE DEVELOPMENT (PHASES 1 AND 2)

ESBA105 (ESBA105, Alcon Research): ESBA105 is a topically administered TNFα inhibitor[25] with highly favorable pharmacokinetic properties. In animal models, ESBA105 in a sodium citrate buffer was administered via eyedrops either in a high frequency (1 drop/hr for up to 10 hours) or multiday (5 drops/d) regimen. ESBA 105 penetrated all ocular compartments in a concentration-dependent manner, reaching therapeutic levels within several hours, with low systemic exposure. Total systemic exposure was approximately 25 000-fold lower when ESBA105 was administered topically as compared to systemic administration. Vitreous ESBA105 concentration was 4.6-fold higher following topical vs systemic administration.[25] A phase 2 pilot study of ESBA105, applied to the eye in hourly dosing intervals with subsequent dose tapering, has been completed in 9 patients with acute anterior uveitis (results were not available as of the publication of this article).[26]

LFG316 (Novartis Pharmaceuticals): LFG316 is a complement inhibitor that targets the complement system at C5. A phase 1 study of intravitreal LFG316 has been completed in patients with advanced age-related macular degeneration.[27] (Results were not available as of the publication of this article.) A phase 2 study to assess intravitreal LFG316 for the treatment of multifocal choroiditis and panuveitis has been planned, but is not yet open for recruitment.[28]

Peptide B27PD (Optiquel; Enzo Biochemical): Peptide B27PD is an HLA class I antigen that mimics ocular S-antigen, thereby directing an immune response toward these antigens in the eye.[29] In a small pilot trial in 9 chronic autoimmune uveitis patients who were treated with peptide B27PD, 4 mg tid for 12 weeks and followed for 5 years, treatment had an ameliorating effect (ie, patients required less immunosuppressive/anti-inflammatory medication for relapses). A decrease in inflammation suggested that tolerance was reinduced. No treatment-related adverse effects were observed (4 patients were retreated over the course of the study.[29] Peptide B27PD is being evaluated in a 52-week, phase 1/2 trial as a corticosteroid-sparing treatment in chronic noninfectious uveitis. The primary end point is time to uveitis recurrence; a key secondary end point is the reduction in total systemic exposure to corticosteroids.[30]

Sotrastaurin (AEB071; Novartis Pharmaceuticals): Sotrastaurin acts as a potent inhibitor of early T-cell activation and β2-integrin-mediated T-cell adhesion. In a 2-week proof-of-concept study involving 32 plaque psoriasis patients, oral sotrastaurin at dosages of 25, 100, 200, or 300 mg bid (cumulative 2-week dosages of 50, 200, 400, and 600 mg/day) improved clinical disease severity as measured on the Psoriasis Area and Severity Index.[31] Adverse effects were generally mild, occurring in 45.8% of the 24 patients receiving sotrastaurin vs 37.5% of the 8 patients receiving placebo.[31] A phase 2 trial in 13 patients with uveitis-associated macular edema was completed in May 2012 (results were not available as of the publication of this article).[32]

At least 3 additional biologic therapies are currently in phase 1 or 2 trials for noninfectious posterior-segment uveitis. Ustekinumab (Janssen Biotech) is an IL-12 inhibitor that is being evaluated in a 52-week pilot trial (N=7) in active, sight-threatening uveitis. Dosing is 90 mg subcutaneous 3 times through week 4 and every 12 weeks thereafter.

The primary outcome is the number of participants who experience at least a 2-step (or down to grade 0) reduction in inflammation on the Standardization of Uveitis Nomenclature (SUN) criteria by week 8.[33]

A small, open-label, 2-year, phase 2 study of abatacept (Bristol-Myers Squibb) is examining changes in visual acuity and vitreous haze, as well as corticosteroid dosage reduction, in patients with steroid-refractory, vision-threatening autoimmune uveitis. Starting doses of 5 mg/kg or 10 mg/kg are being compared with open-label doses of 5-10 mg/kg.[34]

Finally, 5 children and adolescents with uveitis associated with juvenile idiopathic arthritis are being studied in a phase 1/2 trial of tocilizumab (Genentech). The primary outcome is the level of anterior chamber cell control at week 16.[35]

CONCLUSION

Although current treatments for chronic noninfectious uveitis are effective and well-tolerated in many patients, a sizable minority are either suboptimally controlled and/or intolerant of these agents.[4] Fortunately, a number of novel anti-inflammatory agents are currently in clinical development for the treatment of this serious condition. ■

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