Emerging Treatments for Non-infectious Uveitis

Alay S Banker, 1 Carlos Pavesio, 2 and Pauline Merrill 3

1. Banker’s Retina Clinic and Laser Centre, Gujarat, India; 2. Moorfields Eye Hospital, London, UK; 3. Rush University Medical Center, Chicago, IL, US

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The primary goals of treatment in patients with non-infectious uveitis (NIU) are to control ocular inflammation and prevent sight-threatening complications such as macular edema and glaucoma. Systemic corticosteroids are the mainstay of treatment in NIU of the posterior segment (NIU-PS); however, long-term use is associated with treatment-limiting adverse effects. The need for agents with improved safety and tolerability coupled with recent insights into the pathogenesis of NIU-PS have led to the development of novel targeted interventions that potentially reduce or eliminate systemic corticosteroid exposure. Targeted interventions include intraocular drug delivery systems that provide high local concentrations at the site of inflammation with low systemic exposure and therapeutic agents, such as monoclonal antibodies that target specific pro-inflammatory cytokines and cytokine-mediated signaling pathways. The expanding range of therapeutic options enhances the ability to tailor therapy according to individual patient circumstances and optimize outcomes in patients with NIU-PS.

Keywords
Clinical trial, corticosteroid, cytokines, disease management, immunosuppressive agent, intraocular injection, intravitreal, monoclonal antibody, intravitreal, uveitis

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Sarilumab (Kevzara®; Sanofi, Paris, France) is a human monoclonal antibody that binds to the IL-6 receptor and inhibits IL-6-mediated signaling. 10, 15 Sarilumab is currently approved for the treatment of rheumatoid arthritis. 16, 17

Systemic therapies
Evidence from experimental models of uveitis suggests that proinflammatory cytokines such as interleukin (IL)-6 and IL-23 promote the activation and clonal expansion of T helper (T₉) cells, particularly T₉,17 cells, which weaken the blood–retinal barrier and allow leukocytes to enter and damage ocular tissues (Figure 1). 8–10 Studies in patients with uveitis have shown elevated levels of IL-6, IL-10, IL-17, IL-22, IL-23, and tumor necrosis factor alpha (TNF-α), supporting the hypothesis that T₉,17-effector cytokines are central mediators of ocular inflammation and thus potential therapeutic targets. 11 These and other observations have led to the investigation of several systemic agents that target key mediators of inflammatory pathways for the treatment of NIU-PS (Table 1).

Sarilumab
Sarilumab (Kevzara®; Sanofi, Paris, France) is a human monoclonal antibody that binds to the IL-6 receptor and inhibits IL-6-mediated signaling. 10, 15 Sarilumab is currently approved for the...
treatment of rheumatoid arthritis. Animal studies have shown that IL-6-deficient mice are partially protected against induction of experimental autoimmune uveitis, and systemic administration of an anti-IL-6 antibody to mice attenuates experimental autoimmune uveitis. The clinical efficacy of sarilumab in patients with NIU-PS was recently evaluated in Phase II Study to Analyze Sarilumab in Non-infectious Uveitis (SARLINIUSATURN; ClinicalTrials.gov identifier: NCT01900431), a multinational, phase II, randomized, double-masked, placebo-controlled trial. A total of 58 patients received either subcutaneous sarilumab 200 mg or placebo every 2 weeks for 52 weeks. Preliminary results showed no statistically significant difference in the proportion of patients achieving a ≥2-step reduction in vitreous haze (VH) score at week 16, as assessed by a reading center, or a prednisone dose of <10 mg/day (primary endpoint), but suggested a potential benefit in reducing uveitic macular edema. Ocular serious adverse events occurred in one patient (2.6%) in the sarilumab group (uveitis) and one (5.0%) in the placebo group (increased intraocular pressure [IOP]). Final published results from the SARLINIUSATURN study are not yet available.

**Table 1: Investigational systemic therapies for non-infectious uveitis of the posterior segment**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Target/mechanism of action</th>
<th>Dosage</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgotinib (Gilead Sciences, Inc., Foster City, CA, US)</td>
<td>JAK 1 inhibition</td>
<td>200 mg daily, orally</td>
<td>Phase II trial initiated July 2016; results expected July 2022</td>
</tr>
<tr>
<td>Repository corticotropin injection (Mallinkrodt Pharmaceuticals, Hamptom, NJ, US)</td>
<td>ACTH analogue</td>
<td>80 U subcutaneously two or three times weekly</td>
<td>Phase II trial initiated January 2017; results expected December 2019</td>
</tr>
<tr>
<td>Sarilumab (Sanofi SA, Paris, France)</td>
<td>IL-6 inhibition</td>
<td>200 mg subcutaneously every 2 weeks</td>
<td>Phase II trial completed April 2016</td>
</tr>
<tr>
<td>Tocilizumab (Genentech, Inc., San Francisco, CA, US)</td>
<td>IL-6 inhibition</td>
<td>4 or 8 mg/kg monthly</td>
<td>Phase I/I trial completed December 2017</td>
</tr>
<tr>
<td>Ustekinumab (Janssen Biotech, Inc., Horsham, PA, US)</td>
<td>IL-12, IL-23 inhibition</td>
<td>90 mg every 2 weeks</td>
<td>Phase II pilot study initiated September 2016; results expected December 2018</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; IL = interleukin; JAK = Janus kinase.
IL-12 and IL-23, thereby disrupting IL-12- and IL-23-mediated signaling. A phase II, open-label, randomized clinical trial (ClinicalTrials.gov identifier: NCT02931175) evaluating the bioactivity and safety of repository corticocitropin injection in patients with NIU was initiated in January 2017. Patients will receive treatment with repository corticotropin 80 U/day, administered subcutaneously either two or three times per week for up to 12 months. The primary outcome measures include the incidence of ocular and systemic adverse events at 6 and 12 months.

**Intraocular drug delivery**

Targeted delivery of therapeutic agents via intraocular administration yields high therapeutic concentrations at the site of inflammation with potentially lower systemic exposure than oral or intravenous administration. Current routes of intraocular drug delivery include intravitreal injections and corticosteroid implants. Suprachoroidal injections, which utilize the naturally occurring suprachoroidal space between the sclera and choroid as a therapeutic reservoir, represent another potential option.

**Corticosteroid implants**

Intravitreal corticosteroid injections have been shown to improve visual acuity and reduce inflammation in patients with NIU-PS; however, repeated injections are necessary to maintain the effect. Repeated intravitreal injections are generally well tolerated, but have been associated with transient increases in IOP post-injection, cataract formation, endophthalmitis, and retinal detachment. Corticosteroid implants are designed to provide local sustained release of drug over periods ranging from 6 months to 3 years, thereby reducing the need for repeat administration. Two sustained-release corticosteroid implants are currently approved for the treatment of NIU-PS (Retisert®, Bausch + Lomb, Bridgewater, NJ, US; Ozurdex®, Allergan, Inc., Irvine, CA, US) and two additional corticosteroid implants are in late-stage clinical development for the treatment of NIU-PS (YUTIQ™, EyePoint Pharmaceuticals, Inc., Watertown, MA, US; Iluvien®, Alimera Sciences, Inc., Alpharetta, GA, US).

YUTIQ is an injectable intravitreal micro-implant containing 0.18 mg of flucinolone acetonide that provides sustained drug delivery for up to 3 years. In contrast to the surgically implanted 0.59 mg flucinolone device (Retisert), it is implanted via an injection that can be administered in the office setting. Two recent phase III, multicenter, randomized, placebo-controlled trials evaluated the efficacy and safety of the flucinolone acetonide 0.18 mg micro-implant in patients with NIU-PS (ClinicalTrials.gov identifiers: NCT01694186 and NCT02746991). Published results are not yet available; however, pooled 6-month results from the two trials (N=282) presented at the 2018 ARVO meeting showed improvements in the rate of uveitis recurrence (26.6% versus 73.4%; p<0.001) and visual acuity (mean change: +6.0 versus +4.4 letters) in implanted eyes compared with sham-treated eyes. However, IOP elevation of ≥12 mmHg was more common in implanted eyes compared with sham controls (12.2% versus 4.3%). Based on the results of the phase III trials, a New Drug Application was submitted to the US Food and Drug Administration in January 2018.
Iluvien is a non-biodegradable, injectable intravitreal device that uses the same delivery platform as the YUTIQ micro-implant, providing sustained release of 0.19 mg fluocinolone acetonide for up to 3 years. It is currently approved in the United States and Europe for the treatment of diabetic macular edema. Pooled data from two randomized, double-masked, sham-controlled studies in patients with diabetic macular edema showed that Iluvien was generally safe and well tolerated. Cataract surgery was the most common drug-related serious adverse event, occurring in 41.1% and 7.0% of study eyes in the Iluvien and control groups, respectively. In accordance with a licensing and data sharing agreement with EyePoint Pharmaceuticals, an application and control groups, respectively. In accordance with a licensing and data sharing agreement with EyePoint Pharmaceuticals, an application

**Table 2: Investigational local therapeutic agents for non-infectious uveitis of the posterior segment**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of action</th>
<th>Dosage</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluocinolone acetonide intravitreal implant (Allergan Sciences, Inc., Alpharetta, GA, US)</td>
<td>Glucocorticoid receptor agonist</td>
<td>0.19 mg sustained release (~3 years)</td>
<td>Application for NIU-PS indication filed in January 2018*</td>
</tr>
<tr>
<td>Fluocinolone acetonide intravitreal implant (EyePoint Pharmaceuticals, Inc., Watertown, MA, US)</td>
<td>Glucocorticoid receptor agonist</td>
<td>0.18 mg sustained release (~3 years)</td>
<td>Phase III trial completed April 2017</td>
</tr>
<tr>
<td>Suprachoroidal triamcinolone acetonide (Clearside Biomedical, Inc., Alpharetta, GA, US)</td>
<td>Glucocorticoid receptor agonist</td>
<td>4 mg†</td>
<td>Phase III trials completed January 2018</td>
</tr>
<tr>
<td>Intravitreal sirolimus (Santen Inc., Emeryville, CA, US)</td>
<td>mTOR inhibitor</td>
<td>44, 440, or 880 µg bimonthly*</td>
<td>Two phase III trials completed December 2016, third phase III trial in 2018</td>
</tr>
<tr>
<td>Intravitreal infliximab (Janssen Biotech, Horsham, PA, US)</td>
<td>TNF inhibitor</td>
<td>1.5 mg</td>
<td>No active clinical trials in NIU-PS</td>
</tr>
<tr>
<td>Intravitreal ranibizumab (Genentech, Inc. South San Francisco, CA, US)</td>
<td>VEGF inhibitor</td>
<td>0.5 mg†</td>
<td>Phase III trial initiated January 2017</td>
</tr>
<tr>
<td>Intravitreal methotrexate (generic)</td>
<td>Adenosine-mediated leukocyte inhibition</td>
<td>400 µg</td>
<td>Phase III trial initiated January 2017</td>
</tr>
<tr>
<td>Tesidolumab/LFG316 (Novartis Pharmaceuticals, Basel, Switzerland)</td>
<td>CS inhibitor</td>
<td>NR</td>
<td>Phase II trial completed December 2017</td>
</tr>
<tr>
<td>pEYS606 gene therapy (Eyevansys SAS, Paris, France)</td>
<td>Inhibition of TNF expression</td>
<td>NR</td>
<td>Phase I/II trial initiated April 2017</td>
</tr>
</tbody>
</table>

*Application filed in Europe based on data from the phase III trials evaluating the fluocinolone acetonide 0.18 mg intravitreal implant.

†4 mg injection administered at baseline and repeated at week 12 in the phase III clinical trials.

*440 µg selected as the optimal dose based on the phase III clinical trial results.

§0.5 mg injection administered monthly for 3 months in the phase III clinical trial.

CS = complement-5; mTOR = mammalian target of rapamycin; NIU-PS = non-infectious uveitis of the posterior segment; NR = not reported; TNFα = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor.

**Suprachoroidal injection**

Targeted delivery of therapeutic agents to the suprachoroidal space offers the potential advantage of high sustained drug concentrations in the choroid and retina with minimal exposure in other areas of the eye. Two recent trials (Suprachoroidal Injection of CLS-TA in Subjects With Macular Edema Associated With Non-infectious Uveitis [PEACHTREE]; ClinicalTrials.gov identifier: NCT02595398; Suprachoroidal Injection of CLS-TA in Subjects Non-infectious Uveitis [AZALEA]; Clinicaltrials.gov identifier: NCT03097315) investigated the safety and efficacy of 4 mg triamcinolone acetonide administered via suprachoroidal injection using a proprietary injection device (Clearside Biomedical, Alpharetta, GA, US) in patients with NIU (anterior, intermediate, posterior, and panuveitis). PEACHTREE was a phase II, quadruple-masked, sham-controlled trial in 160 patients with macular edema associated with NIU; AZALEA was an open-label safety study in 38 patients with NIU. The trials were completed in January 2018. At the time of writing, published study results were not available; however, in a press release issued in March 2018, the study sponsor announced that the primary endpoint was successfully met in the PEACHTREE trial: ≥15 letter improvement in BCVA at week 24 was observed in 46.9% of patients receiving 4 mg suprachoroidal triamcinolone acetonide every 12 weeks and 15.6% in the sham-control group (p<0.001). Administration of suprachoroidal triamcinolone acetonide resulted in a mean reduction from baseline of 157 microns in central subfield thickness at week 24 versus 19 microns in the sham arm (p<0.001). Treatment was generally well tolerated, although IOP-related adverse events were more common in patients treated with suprachoroidal triamcinolone compared with sham controls (11.5% versus 0%, respectively).

**Intravitreal sirolimus**

Sirolimus is an immunomodulatory agent that inhibits the mammalian target of rapamycin (mTOR), a protein kinase involved in the regulation of T-cell activation, proliferation, and differentiation, and proinflammatory cytokine production. Oral sirolimus is currently approved for the prevention of organ rejection following renal transplant and the treatment of lymphangioleiomyomatosis. A novel intravitreal formulation that delivers therapeutic concentrations to the eye with minimal systemic exposure has been developed by Santen Inc. (Emeryville, CA, US) and evaluated in clinical trials for the treatment of NIU. The trials were completed in January 2018. At the time of writing, published study results were not available; however, in a press release issued in March 2018, the study sponsor announced that the primary endpoint was successfully met in the PEACHTREE trial: ≥15 letter improvement in BCVA at week 24 was observed in 46.9% of patients receiving 4 mg suprachoroidal triamcinolone acetonide every 12 weeks and 15.6% in the sham-control group (p<0.001). Administration of suprachoroidal triamcinolone acetonide resulted in a mean reduction from baseline of 157 microns in central subfield thickness at week 24 versus 19 microns in the sham arm (p<0.001). Treatment was generally well tolerated, although IOP-related adverse events were more common in patients treated with suprachoroidal triamcinolone compared with sham controls (11.5% versus 0%, respectively).
In SAKURA 1,347 patients were randomly assigned to receive one of three doses of intravitreal sirolimus (44, 440, and 880 mg) administered on days 1, 60, and 120. A significantly higher proportion of patients in the 440 mg dose group achieved the primary endpoint of a VH score of 0 at month 5 compared with the 44 mg dose group (22.8% versus 10.3%; p=0.025). Likewise, the proportion of patients achieving the secondary endpoint of a VH score of 0 or 0.5+ was significantly higher in the 440 mg group compared with the 44 mg group (52.6% versus 35%; p=0.008). Comparison between the 880 mg and 44 mg dose groups showed no significant difference in the proportion of patients achieving a VH score of 0 (16.4% versus 10.3%; p=0.182). BCVA improved or was maintained in 80% of patients in all dose groups. Logistic regression analysis showed a higher likelihood of improvement in BCVA in patients in the 440 mg group who had low BCVA at baseline; median improvement was +10.5 letters in patients with baseline BCVA of <20/100 (n=46) versus 1.0 letter in those with baseline BCVA of ≥20/40 (n=149). All three doses appeared to have a corticosteroid-sparing effect; 69.6% of patients who required systemic corticosteroids at baseline were able to taper the dosage to ≤5 mg/day (prednisone equivalent) by month 5. Treatment with intravitreal sirolimus was generally well tolerated. There were no clinically significant changes in mean IOP and treatment-related ocular serious adverse events were uncommon in all three groups.

Collectively, the efficacy and safety results from the first trial suggested that the 440 mg dose offered the most favorable benefit/risk profile in the treatment of NIU-PS. Based on this finding, the protocol for the second trial was amended to terminate further investigation of the 880 mg dose. The primary endpoint (VH=0 at month 5 response) in the 440 mg group in SAKURA 2 was consistent with what was reported in the first trial, but the difference did not reach statistical significance when compared with the 44 mg group (19.1% versus 17.6%; p=0.783). Santen Inc. is planning a new phase III trial evaluating intravitreal sirolimus in patients with NIU-PS.

**Intravitreal infliximab**

Infliximab (Remicade®, Janssen Biotech, Horsham, PA, US) is a chimeric monoclonal antibody to TNF-α that is currently approved for the treatment of a variety of inflammatory and autoimmune conditions. Systemic administration of infliximab is associated with toxicities such as heart failure, exacerbation of multiple sclerosis, and tuberculosis reactivation; however, targeted delivery of infliximab via intravitreal injection results in increased local concentrations with reduced systemic exposure. In a prospective case series including 10 eyes from seven patients with chronic NIU, intravitreal injection of infliximab 1.5 mg improved mean BCVA, VH score, and central macular thickness at 4 weeks. Subsequent analysis of long-term outcomes in the same cohort showed that the benefit was transient; mean BCVA, VH score, and central macular thickness returned to pre-treatment values by month 6. No significant ocular or systemic complications were reported in this series. At the time of writing, there were no active clinical trials evaluating intravitreal infliximab in patients with NIU-PS.

**Intravitreal ranibizumab**

Ranibizumab (Lucentis®, Genentech, San Francisco, CA, US) is a monoclonal antibody that inhibits the biologic activity of vascular endothelial growth factor A. Intravitreal ranibizumab is currently indicated for the treatment of neovascular age-related macular degeneration, retinal vein occlusion, diabetic macular edema, diabetic retinopathy, and myopic choroidal neovascularization. In a prospective case series of seven patients with uveitis and refractory central macular edema, intravitreal ranibizumab (0.5 mg) administered monthly for 3 months resulted in significant improvements in BCVA (mean change: +13 letters; p=0.03) and central retinal thickness (mean change: -357 µm; p=0.03) at 3 months compared with baseline. Most patients required reinjection after 3 months; however, the improvements in BCVA and central retina thickness were maintained at 6 months. Treatment was generally well tolerated, with no evidence of significant ocular or systemic adverse effects. A phase III, randomized comparative trial (Macular Edema Ranibizumab v. Intravitreal Anti-inflammatory Therapy Trial [MERIT], ClinicalTrials.gov identifier: NCT02623426) evaluating treatment with either intravitreal ranibizumab, intravitreal methotrexate, or a dexamethasone implant in 240 patients with NIU-associated macular edema is currently underway and expected to be completed in July 2019.

**Intravitreal methotrexate**

Methotrexate is a cytotoxic agent that exhibits dose-dependent inhibitory effects on neutrophils, macrophages, and T-cells. A pilot study evaluating intravitreal methotrexate (400 µg) in 15 patients with NIU showed statistically significant improvements in visual acuity, VH score, and macular thickness compared with baseline. Five of 13 patients who responded to treatment relapsed after a median duration of 4 months; all four patients who received a repeat injection experienced improved visual acuity following reinjection. Mild ocular pain was the only injection-related adverse event and no patient experienced increased IOP. In a subsequent retrospective case series of 30 patients with NIU, 79% of treated eyes showed improvement in BCVA, ocular inflammation, or central macular thickness over assessment intervals of varying duration. Eight of 30 eyes that responded to initial treatment relapsed (median time to relapse, 3 months); of these eyes, all 8 responded to repeat injection. The median duration of remission in the remaining 22 eyes was 17 months. Eight of 14 patients (57%) who were receiving concomitant therapy with systemic corticosteroids were able to reduce the dose following treatment with intravitreal methotrexate. Treatment appeared to be generally well tolerated; however, adverse events were not prospectively assessed. As noted above, a randomized trial comparing intravitreal methotrexate with either intravitreal ranibizumab or a corticosteroid implant in patients with uveitic macular edema is ongoing.

**Intravitreal tesidolumab/LFG316**

Tesidolumab/LFG316 (Novartis Pharmaceuticals; Basel, Switzerland) is a monoclonal antibody against the complement 5 protein. A recent phase II, multicenter, randomized, controlled, open-label study (ClinicalTrials.gov identifier: NCT01526889) evaluated the safety, efficacy, and pharmacokinetics of intravitreal tesidolumab/LFG316 in patients with active NIU-PS. Patients were randomized to treatment with tesidolumab/LFG316 or conventional immunosuppressive therapy for 12 weeks; patients who met the criteria for treatment response at week 12 were permitted to continue study treatment for an additional 6 months. The study was completed in December 2017; however, published results are not yet available.
The pEYS606 plasmid solution is administered by electrotransfection into the ciliary muscle cells using a proprietary dispersive electroporation device. Ciliary muscle cells exhibit high transfection efficiency and subsequent protein synthesis in various animal models, and preclinical studies have shown pEYS606 to be efficacious in animal models of uveitis.10 A phase I/I, open-label, multicenter, dose-escalation study evaluating the safety, tolerability, and clinical activity of pEYS606 in 20 patients with NIU-PS (ClinicalTrials.gov identifier: NCT03308045) is currently underway in the UK and France, and is expected to be completed in December 2019.

Conclusion

The primary goals of patients with chronic NIU-PS are to achieve durable control of ocular inflammation and prevent sight-threatening complications.1,2 Treatment-limiting systemic adverse effects associated with conventional therapies have prompted the development of therapies that allow targeted local delivery of drugs to the site of inflammation, while insuring the pathogenesis of NIU have led to the emergence of therapies that target specific mediators of autoinflammatory pathways. The expanding range of targeted therapeutic options in development for the management of NIU is promising and will serve to enhance the ability to tailor therapy according to individual patient circumstances, while offering the potential for improved outcomes with reduced systemic exposure to corticosteroids.