A Review of Systemic Biologics and Local Immunosuppressive Medications in Uveitis

Neesurg S. Mehta, MD; Parisa Emami-Naeini, MD, MPH

Department of Ophthalmology and Vision Science, University of California, Davis, Sacramento, CA, USA

ORCID:
Parisa Emami-Naeini: https://orcid.org/0000-0002-4494-7517
Neesurg Mehta: https://orcid.org/0000-0002-7988-9601

Abstract

Uveitis is one of the most common causes of vision loss and blindness worldwide. Local and/or systemic immunosuppression is often required to treat ocular inflammation in noninfectious uveitis. An understanding of safety and efficacy of these medications is required to individualize treatment to each patient to ensure compliance and achieve the best outcome. In this article, we reviewed the effectiveness of systemic biologic response modifiers and local treatments commonly used in the management of patients with noninfectious uveitis.

Keywords: Corticosteroids; Immunosuppression; Uveitis

INTRODUCTION

Uveitis, defined as inflammation in the uveal tract, is a major cause of vision loss and disability especially in the young working-age population.[1] Based on the etiology of inflammation, it can be categorized into infectious or noninfectious uveitis (NIU). The mainstay of treatment in NIU is systemic and/or local immunosuppression.

Systemic therapy with corticosteroids or corticosteroid-sparing immunomodulatory therapy (IMTs) is used for long-term control of uveitis.

These medications achieve sustained control of inflammation while avoiding the risk of peri- or intraocular corticosteroid injections. However, they are associated with an increased risk of systemic infections, malignancies, and other side effects.[1–4] Local treatment, on the other hand, yields faster control of inflammation without causing systemic immunosuppression. These medications, however, are associated with a higher risk of ocular side effects including infection, increased intraocular pressure (IOP), and cataract formation. Often times, a combination of systemic and local treatment is required in order

How to cite this article: Mehta NS, Emami-Naeini P. A Review of Systemic Biologics and Local Immunosuppressive Medications in Uveitis. J Ophthalmic Vis Res 2022;17:276–289.
to achieve appropriate control of inflammation. In this article, we reviewed biologic response modifiers (or biologics) and local treatments used in the management of NIU.

**Systemic Biologics**

Immunomodulatory therapy (IMTs) modifies the immune response and controls inflammation. These medications are divided into conventional IMTs and biologics. Conventional IMTs, including antimetabolites (methotrexate, azathioprine, mycophenolate mofetil) are usually the first-line treatment.\(^1\) Other IMTs include calcineurin inhibitors (cyclosporine, sirolimus, tacrolimus) and alkylating agents (cyclophosphamide, chlorambucil).\(^1\) Biologics are used when NIU is recalcitrant to conventional IMTs and as first-line treatment in select cases.

**Tumor necrosis factor-a inhibitors**

These agents constitute a group of biologics that suppress TNF-a, which is an integral cytokine in the inflammatory cascade.\(^6\) Currently, five TNF-a inhibitors are approved by the United States Food and Drug Administration (FDA) for the treatment of rheumatologic conditions, which include infliximab, adalimumab, golimumab, and certolizumab, all of which are monoclonal TNF-a antibodies, in addition to etanercept, which is a fusion protein that functions as a decoy receptor that binds to TNF-a.\(^5\)

Common side effects of this group of medications include headache, nausea, abdominal pain, diarrhea, constipation, with more severe complications including cytopenia, hepatotoxicity, heart failure, malignancy, and reactivation of infections.\(^6\) Higher risk of demyelinating disorders has been linked to these medications. Hence, they should not be used in patients with history of multiple sclerosis and used with caution if a family history of demyelinating disease is present.\(^7,8\) Anti-TNF-a induced lupus is another complication that is most commonly seen with infliximab use, followed by etanercept and adalimumab.\(^9\) The mechanism is proposed to be autoantibody production secondary to a “cytokine shift” due to anti-TNF-a suppression of T helper 1 response, and hence increasing T helper 2-mediated cytokine and autoantibody production.\(^9\) Treatments involve discontinuation of the anti-TNF-a agents, and sometimes addition of immunosuppressants.\(^9\)

**Infliximab**

Infliximab (Remicade\(^®\)) is an IgG1 chimeric monoclonal antibody against membrane-bound and soluble TNF-a and is administered as an intravenous infusion most commonly at weeks 0, 2, and 6 (induction), and then every eight weeks (maintenance).\(^10\) In uveitis patients, infliximab may be given at a low (<10 mg/kg), moderate (≥10–15 mg/kg), or a high (≥15–20 mg/kg) dose.\(^11\) Efficacy of infliximab has been widely studied in treatment of uveitis associated with Behcet's disease (BD),\(^12–17\) juvenile idiopathic arthritis (JIA),\(^18–22\) sarcoidosis,\(^23\) and other NIUs. These studies have shown an overall clinical efficacy and remission rate of 80–90% for infliximab.\(^24–26\)

In a prospective observational study looking at patients with refractory posterior uveitis receiving infliximab, a complete response was noted in 68% of patients.\(^27\) Another study noted a complete remission in 40% of patients after only three infusions.\(^28\) A retrospective study looking at long-term (>2 years) use of infliximab in patients with refractory JIA-associated uveitis showed clinical remission (defined as no flares for ≥6 months) in ~20% of patients,\(^22\) while another study looking at pediatric patients with refractory NIU noted uveitis control in 89% of patients.\(^20\) In a meta-analysis evaluating efficacy of anti-TNF-a therapy in childhood uveitis, infliximab was found to be effective in 72% of patients.\(^21\)

Response to infliximab (and less commonly, other anti-TNF-a agents) can be adversely affected by the presence of anti-TNF-a antibodies. These antibodies are reportedly seen in ~20% of patients and can cause treatment failure and reaction to infliximab infusions.\(^29\) Concurrent use of immunosuppressant including methotrexate or azathioprine can decrease the risk of autoantibody formation by 50%.\(^29\) Autoantibodies are less commonly seen in adalimumab, which is due to
the fact that adalimumab is a fully humanized molecule.\(^9\)

**Adalimumab**

Adalimumab (Humira\(^9\)) is a fully humanized anti-TNF-a monoclonal antibody and is the only IMT approved by the FDA for use in patients with intermediate, posterior, or panuveitis.\(^{30}\) It is administered subcutaneously 40 mg (or 20 mg if patient’s weight is <30 kg) every other week, often after an initial loading dose of 80 mg.\(^{30}\) It has been commonly used to treat uveitis associated with JIA,\(^{18,21,22,31,32}\) sarcoidosis,\(^{33}\) ankylosing spondylitis (AS),\(^{34}\) and BD,\(^{35}\) in addition to other NIUs.\(^{36–40}\)

In a double-blind, randomized, placebo-controlled trial, the SYCAMORE study group looked at patients on a stable dose of methotrexate with active JIA-associated uveitis and found that the addition of adalimumab resulted in lower rates of treatment failure (27% in the treatment group vs 60% in the control group, \(P<0.0001\)).\(^{31}\) The Visual I Trial, a phase-3 randomized clinical trial, showed that use of adalimumab was associated with a lower rate of uveitis flare and treatment failure in patients with active NIU.\(^{37}\) The VISUAL II Trial was conducted to assess efficacy of adalimumab in inactive NIU and found that treatment failure occurred in 39% of patients treated with adalimumab compared to 55% in the control group, and time to treatment failure was longer in the adalimumab group.\(^{40}\) The VISUAL III trial was a phase-3 open-label extension study involving patients who met treatment failure criteria or those who completed the VISUAL I and II trials and were followed to 78 weeks.\(^{41}\) This study found that 60% of patients with active uveitis and 74% of patients with inactive uveitis achieved quiescence on adalimumab.\(^{41}\)

Although there are no randomized clinical trials comparing the efficacy of infliximab and adalimumab in uveitis, there are many retrospective and observational studies juxtaposing the two anti-TNF-a agents. While several studies have reported similar efficacy between the two drugs in treatment of NIU,\(^{42–44}\) some studies evaluating JIA-associated uveitis have noted better efficacy of adalimumab compared to infliximab.\(^{18,21,22}\) Drug retention rates were similar between the two groups and concomitant use of disease-modifying antirheumatic drugs or treatment history did not affect the retention rates.\(^{45}\) It has also been reported that in the case of loss of initial response of uveitis to one of these two agents, switching to the other one may result in better control of inflammation.\(^{46}\)

**Golimumab**

Golimumab (Simponi\(^9\)), a fully human anti-TNF-a monoclonal antibody, is administered monthly (50 mg) as a subcutaneous injection\(^{47}\) and has been studied in uveitis associated with spondyloarthropathies,\(^{48,49}\) BD,\(^{50,51}\) and other NIUs.\(^{52,53}\) The GO-EASY study looked at patients treated with Golimumab for AS-related uveitis and noted a reduction in acute anterior uveitis rate.\(^{49}\)

**Certolizumab pegol**

Certolizumab (Cimzia\(^9\)) is pegylated Fab fragment of humanized monoclonal antibody against TNF-a.\(^{56}\) It is administered subcutaneously every other week for three injections (400 mg/dose) initially, and then 200 mg every other week.\(^{54}\) It has been studied most commonly in uveitis associated with spondyloarthropathy, in addition to other refractory NIUs.\(^{55–58}\) In an ongoing 96-week open-label phase-4 study, the 48 weeks results revealed an 87% reduction in the incidence of anterior uveitis flare in patients with spondyloarthropathy associated anterior uveitis.\(^{59}\) Similarly, the RAPID-axSpA trial showed a decrease in the frequency of uveitis flares over 96 weeks.\(^{54}\)

**Etanercept**

Etanercept (Enbrel\(^9\)) functions as a decoy receptor for TNF-a.\(^{60}\) Although effective in treating rheumatologic conditions, it is not commonly used for uveitis as it is not as efficacious in comparison to other anti-TNF-a agents,\(^{60}\) and there is risk for drug-induced uveitis and sarcoidosis.\(^{61,62}\)
**Anti-interleukin-1**

**Anakinra and Canakinumab**

Anakinra (Kineret®) is a humanized IL-1 receptor antagonist and Canakinumab (Ilaris®) is an anti-IL-1B monoclonal antibody. They have shown effectiveness in uveitis associated with BD and MS. Adverse reactions to this group of medications include injection site reactions, anaphylaxis, and infections such as pneumonia.

**Gevokizumab**

Gevokizumab (Xoma 052) is a humanized anti-IL-1β monoclonal antibody and is administered intravenously or subcutaneously. It has been studied in uveitis associated with BD and noninfectious scleritis. Although rapid control of BD-related uveitis was noted in the pilot and phase-2 studies, the phase-3 EYEGUARD-B trial failed to meet its primary endpoint and the medicine did not significantly alter the risk of flares.

**Anti-interleukin-2**

**Daclizumab**

Daclizumab (Zinbryta®) is a humanized monoclonal antibody that inactivates T lymphocytes by binding to the CD25 portion of the IL-2 receptor and is administered subcutaneously. Nussenblatt et al. reported that patients with NIU treated with Daclizumab needed less concomitant immunosuppression while maintaining baseline vision at 26 weeks. However, the medicine was withdrawn from the market in 2018 following cases of hepatic injury and meningoencephalitis.

**Anti-IL-interleukin-6**

**Tocilizumab**

Tocilizumab (Actemra®) is a recombinant humanized monoclonal antibody against the IL-6 receptors and is most commonly administered subcutaneously (162 mg every two weeks). An intravenous form is also available. Efficacy of this medicine has been studied in uveitis associated with JIA, BD, uveitic macular edema, and other NIUs. Calvo-Rio et al. found that tocilizumab was effective in treating refractory JIA-associated uveitis, however, the phase-2 APTITUDE trial noted efficacy of only 34% which did not meet the primary endpoint of control of inflammation at week 12. In the STOP-Uveitis study, 37 patients received monthly intravenous infusions of 4 mg/kg or 8 mg/kg of tocilizumab over six months and found that 43% of patients had two-step decrease in vitreous haze and 30% gained two lines or more vision, although there was no statistically significant difference in vision and central macular thickness (CMT) between two doses. Common side effects include injection site reactions, arthralgia, and headaches.

**Sarilumab**

Sarilumab (Kevzara®) is a human monoclonal antibody blocking the IL-6 receptor and is commonly administered subcutaneously. The phase-2 SATURN study evaluated the efficacy and safety of Sarilumab over 16 weeks in patients with intermediate, posterior, or panuveitis. This study found that in comparison to the placebo group, patients taking Sarilumab achieved a statistically significant reduction in use of corticosteroids or at least two-step reduction in vitreous haze when assessed by investigators (64.0% vs 35.0%, \( P = 0.03 \)), but not when assessed based on fundus photography and by central reading center (46.1 vs 30.0%, \( P = 0.2 \)). The most common adverse reactions include injection site reactions, respiratory tract infection, urinary infections, nasopharyngitis, transaminitis, while more severe adverse reactions include neutropenia and infections.

**Anti-interleukin-17**

Secukinumab (Cosentyx®) is a fully human monoclonal antibody against IL-17A and is administered subcutaneously. Three phase-III trials examined the efficacy of Secukinumab in patients with BD-associated uveitis, active NIU, and quiescent NIU. None of these studies showed a statistically significant difference in uveitis recurrence between Secukinumab and placebo. The most common adverse reactions include...
headache, diarrhea, upper respiratory infections, neutropenia, inflammatory bowel disease, and malignancy.\textsuperscript{[88]}

**Anti-interleukin-23**

Ustekinumab (Stelara\textsuperscript{®}) is a humanized monoclonal antibody against IL-12 and IL-23 and is administered most commonly subcutaneously.\textsuperscript{[89]} Studies have reported successful control of uveitis associated with psoriatic arthritis, plaque psoriasis,\textsuperscript{[90]} and Crohn's disease.\textsuperscript{[91]} Adverse reactions include headache, fatigue, injection site reaction, upper respiratory infections, urinary tract infections, malignancy, and cardiovascular events.\textsuperscript{[89]}

**Anti-CD20**

Rituximab (Rituxan\textsuperscript{®}) is a humanized monoclonal antibody against CD20 and is administered intravenously.\textsuperscript{[92–96]} It has been studied in uveitis associated with BD,\textsuperscript{[96, 97]} JIA,\textsuperscript{[93, 98]} noninfectious scleritis,\textsuperscript{[99–101]} granulomatosis with polyangiitis,\textsuperscript{[102–106]} Vogt-Koyanagi-Harada disease (VKH),\textsuperscript{[107]} Susac syndrome,\textsuperscript{[108]} in addition to other NIUs.\textsuperscript{[92, 103, 110]} Lasave et al reported on 21 eyes with refractory noninfectious posterior uveitis of which 82% achieved control of inflammation on fluorescein angiography at two years.\textsuperscript{[92]} Cao et al examined patients with refractory noninfectious scleritis and found that 86.6% of cases achieved scleritis activity score of zero at month six.\textsuperscript{[99]} Common adverse reactions include infusion reaction (fever, rigor, and chills), while more severe side effects include infections, progressive multifocal leukoencephalopathy, and hepatitis B reactivation.\textsuperscript{[110]}

**Selective costimulation modulator**

Abatacept (Orencia\textsuperscript{®}) is a recombinant fusion protein made up of the extracellular domain of human cytotoxic T-lymphocyte antigen 4 (CTLA-4) and fragment of Fc domain of human IgG.\textsuperscript{[111]} This molecule competitively inhibits antigen-presenting cells (APCs) from binding to CD80 and CD86 on T cells, hence, preventing APCs from delivering a co-stimulatory response and activating T cells.\textsuperscript{[111]} Studies have shown that Abatacept can be effective in controlling JIA-associated uveitis.\textsuperscript{[112–115]} Common side effects include headache, upper respiratory tract infection, and nausea while serious adverse reactions include infection.\textsuperscript{[116, 117]}

**Interferons**

Interferons have been studied widely in the treatment of NIU,\textsuperscript{[118]} especially in BD-associated uveitis.\textsuperscript{[119–125]} Studies have found that IFN-alpha is effective in 84–92% of patients with BD-associated posterior or panuveitis\textsuperscript{[121, 123]} as well as uveitic macular edema\textsuperscript{[126, 127]} and macular edema related to presumed ocular tuberculosis.\textsuperscript{[128, 129]} IFN-beta has shown effectiveness in reducing macular edema and improving vision in intermediate uveitis-associated macular edema.\textsuperscript{[130]} Common adverse effects include nausea, fatigue, flu-like symptoms, psychiatric sequelae, elevated transaminases, and hematologic toxicity.\textsuperscript{[118, 131]}

**Janus kinase inhibitors**

Tofacitinib (Xeljanz\textsuperscript{®}) is a small molecule that reversibly inhibits Janus-associated kinases (JAKs).\textsuperscript{[132]} JAKs mediate cytokine receptor signaling, initiating a downstream pathway which eventually leads to transcription of inflammatory genes.\textsuperscript{[132]} In a case of JIA-associated uveitis only responsive to intravitreal dexamethasone implants, tofacitinib successfully controlled the uveitis and arthritis, and the patient no longer required corticosteroid implants.\textsuperscript{[133]} Similarly, Misrocchi et al.\textsuperscript{[134]} reported on four cases of refractory JIA-associated uveitis and noted a good uveitis response, though a less favorable arthritis response when treated with JAK inhibitors. Paley et al.\textsuperscript{[132]} reported one case of refractory anterior and intermediate uveitis and another case of refractory scleritis treated successfully with JAK inhibitors. Common adverse effects include upper respiratory infection, diarrhea, headache, and malignancy.\textsuperscript{[135]}

**Local Treatments**

Peri- or intraocular administration of immunosuppressives can provide a high dose
of medication to the posterior segment of the eye while avoiding systemic side effects. These medications are more commonly used in unilateral uveitis.

**Periocular or intraocular corticosteroid injections**

Local corticosteroids have been widely studied in the treatment of uveitis. These medications are effective at local control of inflammation. Side effects include ocular infection, cataract formation and increase in IOP.\(^\text{[136]}\)

**Triamcinolone acetonide**

Triamcinolone acetonide (TA) can be administered adjacent but outside the globe in the posterior sub-Tenon space through the orbital septum (Kenalog\textsuperscript{®} 40 mg/ml, Bristol-Myers Squibb Company, Princeton, NJ) or in the vitreous cavity (Triesence\textsuperscript{®} 40 mg/ml, Alcon Pharmaceuticals, Fort Worth, TX). Triesence\textsuperscript{®} is preservative-free and more expensive than the preserved formulation (Kenalog\textsuperscript{®}). Sub-Tenon's TA typically lasts two to three months, although this can be variable due to variable crystal sizes. Intravitreal TA crystals are more uniformly sized, hence, Triesence\textsuperscript{®} has a more predictable duration of action of four to six weeks (less in vitrectomized eyes).\(^\text{[136]}\) Effectiveness of these steroids has been studied extensively.\(^\text{[137]}\) It has been demonstrated that both injections are effective in patients with NIU, however, intravitreal corticosteroids were more effective in improving vision and macular edema, although a significantly higher risk of IOP elevation was associated with intravitreal corticosteroids compared to periocular injection.\(^\text{[137]}\)

**Dexamethasone intravitreal implant**

The Dexamethasone implant (Ozurdex\textsuperscript{®}) is a bioerodible, sustained release injectable implant that gradually releases dexamethasone into the posterior chamber and usually lasts three to four months.\(^\text{[138]}\) It is FDA approved for use in patients with posterior segment inflammation. In a prospective, randomized, controlled clinical trial, the HURON Study group looked at patients with noninfectious intermediate or posterior uveitis who were randomized to receive dexamethasone implant (0.7 mg or 0.35 mg) or sham.\(^\text{[138]}\) At week eight (primary endpoint), patients in the dexamethasone implant group experienced significant reduction in vitreous haze and CMT compared to the control group. The percentage of eyes gaining >15 letters was two- to sixfolds higher in the implant groups as compared to the sham group. Less than 5% of the eyes developed IOP of >35 mmHg across all groups. Other side effects included cataract formation (as high as 29% after 12 months) and migration of implant to the anterior chamber, which caused corneal decompensation.\(^\text{[139]}\)

**Fluocinolone acetonide intravitreal implant (injectable)**

The fluocinolone acetonide intravitreal implant (Yutiq\textsuperscript{®}) (FAi) is a non-bioerodible injectable intravitreal implant containing 0.18 mg fluocinolone acetonide. It is designed to release the steroid over 36 months and is FDA approved for noninfectious posterior uveitis.\(^\text{[140]}\) In a large prospective, randomized, sham-controlled trial, Jaffe et al.\(^\text{[140]}\) evaluated 129 patients with chronic noninfectious posterior uveitis over three years who received either the FAi or sham. At 36 months, the recurrence rate was 5.7% in FAi group versus 28.6% in sham group (\(P < 0.001\)) and the median time to first recurrence was significantly lower in the FAi group (657 days vs 70.5 days, respectively).\(^\text{[141]}\) About 11.9% of the patients in the FAi group required glaucoma surgery (compared to 5.7% in the sham group) and as expected most patients (73.8%) in the FAi group required cataract surgery (compared to 23.8% in the sham group).\(^\text{[141]}\)

**Fluocinolone acetonide implant (surgical)**

The Retisert\textsuperscript{®} implant contains 0.59 mg fluocinolone acetonide (releasing approximately 2 µg/day for three years) and is implanted through the pars plana in the vitreous cavity during surgery.\(^\text{[142]}\) The Multicenter Uveitis Steroid Treatment (MUST) trial compared this implant
to systemic immunosuppression and found that although the implant group showed improved visual acuity and uveitis control at two years,[142] the opposite was true at seven years.[143] This should be interpreted with caution as majority of patients who received the implant did not receive an additional implant and a significant number of patients were lost to follow-up or received cross-over treatment.

**Suprachoroidal corticosteroids**

Administration of drugs in the suprachoroidal space (between choroid and sclera) has been investigated as an alternate technique for targeted delivery of molecules to the posterior chorioretinal structures.[144] An investigational corticosteroid formulation (preservative-free TA, CLS-TA, Clearside Biomedical, Alpharetta, Georgia, USA) injected into the suprachoroidal space has been studied in patients with uveitic macular edema. Safety and efficacy of this formulation was studied in an open label safety trial (AZALEA trial) and phase-3 randomized trial (PEACHTREE trial).[145,146] These studies showed a statistically significant reduction in macular edema and improvement in visual acuity in the treatment arm compared to the control group, without a significant increase in the rate of cataract formation or IOP.[146] This special formulation (Xipere™, TA injectable suspension 40 mg/ml, Bauch + Lomb and Clearside Biomedical) injected via the proprietary Microinjector® recently received FDA approval for use in the treatment of uveitis macular edema.

**Non-steroidal injections**

**Methotrexate**

Methotrexate was the first systemic non-steroidal IMT that received FDA approval for use in autoimmune disease.[147] Efficacy of intravitreally administered methotrexate in patients with noninfectious uveitis has been reported in retrospective studies.[148,149] Safety and efficacy of this drug in patients with macular edema is currently under investigation in the Macular Edema Ranibizumab versus Intravitreal Anti-inflammatory Therapy (MERIT) multicenter, randomized controlled.[150] Intravitreal methotrexate is also used in patients with vitreoretinal lymphoma.[151] Side effects include risk of infection and corneal epitheliopathy.[151]

**Sirolimus**

Sirolimus is an inhibitor of the mammalian target of rapamycin and downstream production of proinflammatory cytokines.[152,153] The one-year results from the SAVE1 study showed that although intravitreal formulation was better tolerated, there was no difference in efficacy between subconjunctival and intravitreal administration of Sirolimus in treatment of noninfectious intermediate, posterior or panuveitis.[153,154] The SAVE2 trial illustrated that monthly injections of 440 µg intravitreal Sirolimus was better at reducing vitreous haze, CMT, and improving vision when compared to the 880 µg bimonthly dose.[155] In a combined analysis of 592 patients in phase-3 trials, SAKURA1 and -2, Merrill et al.[152] showed that a significantly higher proportion of patients treated with intravitreal Sirolimus 440 µg compared with 44 µg achieved vitreous haze of 0 at five months, though there were similar percentages of patients with >5 letter improvement in vision and those tapered off corticosteroids in both dose groups.

**Anti-TNF agents**

Efficacy and safety of intravitreal infliximab was studied in animal models and human studies.[156–159] Human studies reported variable efficacy of intravitreal infliximab in controlling inflammation but raised safety concerns, including development of intraocular inflammatory response,[156] decreased electroretinogram amplitudes, and visual field measurements.[157] Intravitreal adalimumab has shown effectiveness in controlling inflammation and macular edema in small retrospective studies.[160,161] More studies are required to evaluate long-term safety and efficacy of intravitreally administered medicine.
Intravitreally administered Rituximab (alone or together with methotrexate) is widely used and proven effective in patients with vitreoretinal lymphoma. Side effects include transient IOP elevation and iridocyclitis.

Novel Technologies: Electroporation

The biotechnology company Eyevensys (Paris, France) has created the first gene expression technology that uses plasmids to induce production of cytokines. Using a small needle, the device inserts plasmids into the ciliary muscle and a series of short electrical pulses induce uptake of these plasmids into the cells. EYS606 is a treatment being investigated in an ongoing phase-I/II trial (NCT03308045) in the European Union for treatment of NIU by introducing a plasmid encoding for TNF-α inhibitors. Preliminary study included nine patients receiving escalating doses of the EYE606 treatment. One patient noted a ≥10 letter gain in vision after two weeks and two patients noted a ≥20% reduction in macular edema and ≥12 letter gain in vision after six to eight months. The ongoing part two of the study will assess safety and efficacy of the highest and maximally tolerated EYS606 dose over 48 weeks. The Electro Study ((NCT03308045) is an ongoing phase-2 trial in the US assessing safety and efficacy of two doses of EYS606.

Common Practice and Future Horizons

Systemic and/or local immunosuppression are mainstay of treatment in NIU and usually a combination of these modalities is needed to control inflammation and achieve quiescence. In systemic management of uveitis, a “stepladder” approach is recommended. This approach starts with local and/or systemic corticosteroids followed by IMTs (as needed) with the goal of reducing the dose of systemic corticosteroids to <5–10 mg of prednisone per day. Patients with chronic uveitis need to be counselled on the need for long-term treatment, the different options available to them, and the side effects of systemic and local therapeutics, all in an effort to tailor treatment to each patient and increase long-term compliance. The advent of novel local and systemic treatment options has decreased the risk of breakthrough inflammation and long-term vision loss in patients with NIU.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. You C, Sahawneh HF, Ma L, Kubaisi B, Schmidt A, Foster CS. A review and update on orphan drugs for the treatment of noninfectious uveitis. Clin Ophthalmol 2017;11:257–265.
2. Durnian JM, Stewart RM, Tatham R, Batterbury M, Kaye SB. Cyclosporin-A associated malignancy. Clin Ophthalmol 2007;1:421–430.
3. O’Neill JO, Edwards LB, Taylor DO. Mycophenolate mofetil and risk of developing malignancy after orthotopic heart transplantation: analysis of the transplant registry of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:1186–1191.
4. Kempen JH, Daniel E, Dunn JP, Foster CS, Gangaputra S, Hanish A, et al. Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study. BMJ 2009;339:b2480.
5. Leal I, Rodrigues FB, Sousa DC, Duarte GS, Romão VC, Marques-Neves C, et al. Anti-TNF drugs for chronic uveitis in adults—a systematic review and meta-analysis of randomized controlled trials. Front Med 2019;6:104.
6. Aziz M, Fatima R. Infliximab [Internet]. Treasure Island, FL: StatPearls Publishing; 2022 [updated 2021 Jul 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500021/
7. van Oosten BW, Barkhof F, Truyen L, Boringa JB, Bertelsmann FW, von Blomberg BM, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology 1996;47:1531–1534.
8. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology 1999;53:457–465.
9. Almoallim H, Al-Ghamdi Y, Almaghrabi H, Alyasi O. Anti-tumor necrosis factor-α induced systemic lupus erythematosus. Open Rheumatol J 2012;6:315–319.
10. Kruh JN, Yang P, Suelves AM, Foster CS. Infliximab for the treatment of refractory noninfectious uveitis: a study of 88 patients with long-term follow-up. *Ophthalmology* 2014;121:358–364.

11. Sukumaran S, Marzan K, Shaham B, Reiff A. High dose infliximab in the treatment of refractory uveitis: does dose matter? *ISRN Rheumatol* 2012;2012:765380.

12. Cantini F, Niccoli L, Nannini C, Kaloudi O, Cassarè A, Susini M, et al. Efficacy of infliximab in refractory Behçet’s disease-associated and idiopathic posterior segment uveitis: a prospective, follow-up study of 50 patients. *Biologics* 2012;65:12.

13. El Garf AK, Shahin AA, Shawky SA, Azim MA, Effat DA, Abdelrahman SK. Efficacy of infliximab in refractory posterior uveitis in Behçet’s disease patients. *The Egyptian Rheumatologist* 2018;40:93–97.

14. Keino H, Okada A, Watanabe T, Taki W. Long-term efficacy of infliximab on background vascular leakage in patients with Behçet’s disease. *Eye* 2014;28:1100–1106.

15. Fabiani C, Sota J, Vitale A, Emmi G, Vannozzi L, Bacherini D, et al. Ten-year retention rate of infliximab in patients with Behçet’s disease-related uveitis. *Ocul Immunol Inflamm* 2019;27:34–39.

16. Giardina A, Ferrante A, Ciccio F, Vadalà M, Giardina E, Triolo G. One year study of efficacy and safety of infliximab in the treatment of patients with ocular and neurological Behçet’s disease refractory to standard immunosuppressive drugs. *Rheumatol Int* 2011;31:33–37.

17. Okada AA, Goto H, Ohno S, Mochizuki M, Ocular Behçet’s Disease Research Group of Japan. Multicenter study of infliximab for refractory uveoretinitis in Behçet disease. *Arch Ophthalmol* 2012;130:592–598.

18. Constantin T, Foeldvari I, Anton J, de Boer J, Czitrom-Guillaume S, Edelsten C, et al. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. *Ann Rheum Dis* 2018;77:1107–1117.

19. Richards JC, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Exp Ophthalmol* 2005;33:461–468.

20. Miraldi Utz V, Bulas S, Lopper S, Fenchel M, Sa T, Mehta M, et al. Effectiveness of long-term infliximab use and impact of treatment adherence on disease control in refractory, non-infectious pediatric uveitis. *Pediatr Rheumatol Online J* 2019;17:79.

21. Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti–tumor necrosis factor α treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. *Arthritis Care Res* 2014;66:1073–1084.

22. Cecchin V, Zannin ME, Ferrari D, Pontikaki I, Misericocchi E, Paroli MP, et al. Long-term safety and efficacy of adalimumab and infliximab for uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2018;45:1167–1172.

23. Baughman RP, Bradley DA, Lower EE. Infliximab in chronic ocular inflammation. *Int J Clin Pharmacol Ther* 2005;43:7–11.

24. Naganuma M, Sakuraba A, Hisamatsu T, Ochiai H, Hasegawa H, Ogata H, et al. Efficacy of infliximab for induction and maintenance of remission in intestinal Behçet’s disease. *Inflamm Bowel Dis* 2008;14:1259–1264.

25. Sharma PK, Markov GT, Bajwa A, Foster CS. Long-term efficacy of systemic infliximab in recalcitrant retinal vasculitis. *Retina* 2015;35:2641–2446.

26. Maleki A, Sahawneh HF, Ma L, Meese H, He Y, Foster CS. Infliximab therapy in patients with infectious intermediate uveitis resistant to conventional immunomodulatory therapy. *Retina* 2017;37:836–843.

27. Cantini F, Niccoli L, Nannini C, Kaloudi O, Cassarè A, Susini M, et al. Efficacy of infliximab in refractory Behçet’s disease-associated and idiopathic posterior segment uveitis: a prospective, follow-up study of 50 patients. *Biologics* 2012;6:5–12.

28. El Garf AK, Shahin AA, Shawky SA, Azim MA, Effat DA, Abdelrahman SK. Efficacy of infliximab in refractory posterior uveitis in Behçet’s disease patients. *The Egyptian Rheumatologist* 2018;40:93–97.

29. Lee LY, Sanderson JD, Irving PM. Anti-infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis. *Eur J Gastroenterol Hepatol* 2012;24:1078–1085.

30. LaMattina KC, Goldstein DA. Adalimumab for the treatment of uveitis. *Expert Rev Clin Immunol* 2017;13:181–188.

31. Ramanan AV, Dick AD, Jones AP, Hughes DA, McKay A, Rosala-Hallas A, et al. Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT. *Health Technol Assess* 2019;23:1–140.

32. Horton S, Jones AP, Guly CM, Hardwick B, Beresford MW, Lee RW, et al. Adalimumab in juvenile idiopathic arthritis-associated uveitis: 5-year follow-up of the Bristol participants of the SYCAMORE trial. *Am J Ophthalmol* 2019;207:170–174.

33. Erkens RJ, Mostard RL, Wijnen JD, Schouten JS, Drent M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. *Graefes Arch Clin Exp Ophthalmol* 2012;250:713–720.

34. Rudwaleit M, Reddevand E, Holck P, Vanhoof J, Kron M, Kary S, et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. *Ann Rheum Dis* 2009;68:696–701.

35. Fabiani C, Vitale A, Emmi G, Vannozzi L, Lopalco G, Guerriero S, et al. Efficacy and safety of adalimumab in Behçet’s disease-related uveitis: a multicenter retrospective observational study. *Clin Rheumatol* 2017;36:183–189.

36. Suhler EB, Lowder CY, Goldstein DA, Giles T, Lauer AK, Kurz PA, et al. Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. *Br J Ophthalmol* 2013;97:481–486.

37. Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, et al. Adalimumab in patients with active noninfectious uveitis. *N Engl J Med* 2016;375:932–943.

38. Diaz-Llopis M, Salom D, Garcia-de-Vicuña C, Cordero-Coma M, Ortega G, Ortego N, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. *Ophthalmology* 2012;119:1575–1581.

39. Dobner BC, Max R, Becker MD, Heinz C, Veltrup I, Heiligenhaus A, et al. A three-centre experience with adalimumab for the treatment of non-infectious uveitis. *Br J Ophthalmol* 2013;97:134–138.
40. Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet* 2016;388:1183–1192.

41. Suhler EB, Adán A, Brézin AP, Fortin E, Goto H, Jaffe GJ, et al. Safety and efficacy of adalimumab in patients with noninfectious uveitis in an ongoing open-label study: VISUAL III. *Ophthalmology* 2018;125:1075–1087.

42. Lejoyeux R, Diwo E, Vallet H, Saadoun D, Tezenas du Montcel S, Bodaghi B, et al. INFliximAB and ADALIMUMAB in uveitic macular edema. *Ocul Immunol Inflamm* 2018;26:991–996.

43. Vallet H, Seve P, Biard L, Baptiste Fraison J, Bielefeld P, Perard L, et al. Infliximab versus adalimumab in the treatment of refractory inflammatory uveitis: a multicenter study from the French uveitis network. *Arthritis Rheumatol* 2016;68:1522–1530.

44. Martel JN, Esterberg E, Nagpal A, Acharya NR. Infliximab and adalimumab for uveitis. *Ocul Immunol Inflamm* 2012;20:18–26.

45. Fabiani C, Vitale A, Emmi G, Bitossi A, Lopalo G, Sota J, et al. Long-term retention rates of adalimumab and infliximab in non-infectious intermediate, posterior, and panuveitis. *Clin Rheumatol* 2019;38:63–70.

46. Dhingra N, Morgan J, Dick AD. Switching biologic agents for uveitis. *Eye* 2009;23:1866–1870.

47. Boyce EG, Halliwell J, Stan-Ugboe O. Golimumab: review of the efficacy and tolerability of a recently approved tumor necrosis factor-α inhibitor. *Clin Ther* 2010;32:1681–1703.

48. Calvo-Rio V, Blanco R, Santos-Gómez M, Rubio-Romero E, Cordero-Coma M, Gallego-Flores A, et al. Golimumab in uveitic patients with spondyloarthritis. Multicenter study of 15 patients. *Semin Arthritis Rheum* 2016;46:95–101.

49. van Bentum RE, Heslinga SC, Nurmohamed MT, Gerard AH, Grieb EN, Koehorst CBJM, et al. Reduced occurrence rate of acute anterior uveitis in ankylosing spondylitis treated with golimumab - the GO-EASY study. *J Rheumatol* 2019;46:153–159.

50. Fabiani C, Sota J, Rigante D, Vitale A, Emmi G, Vannozzi L, et al. Rapid and sustained efficacy of golimumab in the treatment of multifracte uveitis associated with Behçet’s disease. *Ocul Immunol Inflamm* 2019;27:58–63.

51. Vitale A, Emmi G, Lopalo G, Fabiani C, Gentileschi S, Silvestri E, et al. Long-term efficacy and safety of golimumab in the treatment of multifracte uveitis associated with Behçet’s disease. *Clin Rheumatol* 2017;36:2063–2069.

52. Cordero-Coma M, Calvo-Rio V, Adán A, Blanco R, Álvarez-Castro C, Mesquida M, et al. Golimumab as rescue therapy for refractory immune-mediated uveitis: a three-center experience. *Mediators Inflamm* 2014;2014:717598.

53. Miserochi E, Modarati G, Pontikaki I, Meroni PL, Gerlioni V. Long-term treatment with golimumab for severe uveitis. *Ocul Immunol Inflamm* 2014;22:90–95.

54. Rudwaleit M, Rosenbaum JT, Landewé R, Marzo-Ortega H, Sieper J, van der Heijde D, et al. Observed incidence of uveitis following certolizumab pegol treatment in patients with axial spondyloarthritis. *Arthritis Care Res* 2016;68:838–844.

55. Gómez-Santos M, Llorenç V, Mesquida M, Blanco R, Calvo-Rio V, Maiz O, et al. Efficacy of certolizumab in patient with refractory uveitis to other biologic therapy. Study of 7 cases [1251]. Abstract presented at: 2014 ACR/ARHP Annual Meeting; 2014 Nov 14–19; Boston, MA.

56. Sharon Y, Chu DS. Certolizumab pegol - tumor necrosis factor inhibitor for refractory uveitis. *Am J Ophthalmol Case Rep* 2020;18:100633.

57. Llorenc V, Mesquida M, Sainz de la Maza M, Blanco R, Calvo V, Maiz O, et al. Certolizumab pegol, a new anti-TNF-α in the armamentarium against ocular inflammation. *Ocul Immunol Inflamm* 2016;24:167–172.

58. Tosi GM, Sota J, Vitale A, Rigante D, Emmi G, Lopalo G, et al. Efficacy and safety of certolizumab pegol and golimumab in the treatment of non-infectious uveitis. *Clin Exp Rheumatol* 2019;37:680–683.

59. van der Horst-Bruinsma I, van Bentum R, Verbraak FD, Rath T, Rosenbaum JT, Misterska-Skora M, et al. The impact of certolizumab pegol treatment on the incidence of anterior uveitis flares in patients with axial spondyloarthritis: 48-week interim results from C-VIEW. *RMD Open* 2020;6:e001161.

60. Foster CS, Tufail F, Waheed NK, Chu D, Miserochi E, Baltatzis S, et al. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. *Arch Ophthalmol* 2003;121:437–440.

61. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. *Arthritis Rheum* 2007;56:3248–3252.

62. Iqbal KM, Hay MW, Emami-Naeini P. Medication-induced uveitis: an update. *J Ophthalmic Vis Res* 2021;16:84–92.

63. Sota J, Vitale A, Insalaco A, Sfriso P, Lopalo G, Emmi G, et al. Safety profile of the interleukin-1 inhibitors anakinra and canakinumab in real-life clinical practice: a nationwide multicenter retrospective observational study. *Clin Rheumatol* 2018;37:2233–2240.

64. Dinarello CA, Simon A, van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov* 2012;11:633–652.

65. Fabiani C, Vitale A, Emmi G., Lopalo G, Vannozzi L, Guerriero S, et al. Interleukin (IL)-1 inhibition with anakinra and canakinumab in Behçet’s disease-related uveitis: a multicenter retrospective observational study. *Clin Rheumatol* 2017;36:191–197.

66. Fabiani C, Vitale A, Rigante D, Emmi G, Lopalo G, Di Scala G, et al. The presence of uveitis is associated with a sustained response to the interleukin (IL)-1 inhibitors anakinra and canakinumab in Behçet’s disease. *Ocul Immunol Inflamm* 2020;28:298–304.

67. Uğurlu S, Ucar D, Seyahi E, Hatemi G, Yurdakul S. Canakinumab in a patient with juvenile Behçet’s syndrome with refractory eye disease. *Ann Rheum Dis* 2012;71:1589–1591.

68. Lopalo G, Schiraldi S, Venerito V, Guerriero S, Iannone F. Effectiveness and safety profile of anakinra in a HLA-B27 positive patient with multiple sclerosis-associated uveitis. *Mult Scler Relat Disord* 2020;42:102152.

69. Sota J, Vitale A, Insalaco A, Sfriso P, Lopalo G, Emmi G, et al. Safety profile of the interleukin-1 inhibitors anakinra and canakinumab in real-life clinical practice: a nationwide multicenter retrospective observational study. *Clin Rheumatol* 2018;37:2233–2240.
70. Gül A, Tugal-Tutkun I, Dinarello CA, Reznikov L, Esen BA, Mirza A, et al. Interleukin-1β-regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behçet's disease: an open-label pilot study. Ann Rheum Dis 2012;71:563–566.

71. Tugal-Tutkun I, Kadayifcilar S, Khairallah M, Lee SC, Ozdal P, Özyazgan Y, Song JH, et al. Safety and efficacy of gevokizumab in patients with Behçet’s disease uveitis: results of an exploratory phase 2 study. Ocul Immunol Inflamm 2017;25:62–70.

72. Tugal-Tutkun I, Pavesio C, De Cordoue A, Bernard-Poenaru O, Gül A. Use of gevokizumab in patients with Behçet’s disease uveitis: an international, randomized, double-masked, placebo-controlled study and open-label extension study. Ocul Immunol Inflamm 2018;26:1023–1033.

73. Knickelbein JE, Tucker WR, Bhatt N, Armbust K, Valient D, Obiyor D, et al. Gevokizumab in the treatment of autoimmune non-necrotizing anterior scleritis: results of a phase II/III clinical trial. Am J Ophthalmol 2016;172:104–110.

74. Wroblewski K, Sen HN, Yeh S, Faia L, Li Z, Sran P, et al. Long-term daciizumab therapy for the treatment of noninfectious ocular inflammatory disease. Can J Ophthalmol 2011;46:322–328.

75. Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF, Letko E, et al. Initial evaluation of subcutaneous daciizumab treatments for noninfectious uveitis: a multicenter noncomparative interventional case series. Ophthalmology 2005;112:764–770.

76. Brooks M. MS drug daciizumab (Zinbryta) pulled from the market [Internet]. Medscape; 2018. Available from: https://www.medscape.com/viewarticle/893352

77. Ramanan AV, Dick AD, Guly C, McKay A, Jones AP, Hardwick B, et al. Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial. Lancet Rheumatol 2020;2:e135–e141.

78. Calvo-Rio V, Santos-Gómez M, Calvo I, González-Fernández MI, López-Montesinos B, Mesquida M, et al. Anti-Interleukin-6 receptor tocilizumab for severe juvenile idiopathic arthritis-associated uveitis refractory to tumor necrosis factor therapy: a multicenter study of twenty-five patients. Arthritis Rheumatol 2017;69:668–675.

79. Atienza-Mateo B, Calvo-Rio V, Beltrán E, Martínez-Costa L, Valls-Pascual E, Hernández-Garfella M, et al. Anti-interleukin-6 receptor tocilizumab in refractory uveitis associated with Behçet's disease: multicentre retrospective study. Rheumatology 2018;57:856–864.

80. Adán A, Mesquida M, Llorenç V, Espinosa G, Molins B, Hernández MV, et al. Tocilizumab treatment for refractory uveitis-related cystoid macular edema. Graefes Arch Clin Exp Ophthalmol 2013;251:2627–2632.

81. Deuter CME, Zierhut M, Igney-Oertel A, Xentidis T, Feidt A, Sobolewska B, et al. Tocilizumab in uveitic macular edema refractory to previous immunomodulatory treatment. Ocul Immunol Inflamm 2017;25:215–220.

82. Mesquida M, Molins B, Llorenç V, Hernández MV, Espinosa G, Sainz de la Maza M, et al. Twenty-four month follow-up of tocilizumab therapy for refractory uveitis-related macular edema. Retina 2018;38:1361–1370.

83. Vegas-Revenga N, Calvo-Rio V, Mesquida M, Adán A, Hernández MV, Beltrán E, et al. Anti-IL6-receptor tocilizumab in refractory and noninfectious uveitic cystoid macular edema: multicenter study of 25 patients. Am J Ophthalmol 2019;200:85–94.

84. Sepah YJ, Sadiq MA, Chu DS, Dacey M, Gallemore R, Dayani P, et al. Primary (month-6) outcomes of the STOP-uveitis study: evaluating the safety, tolerability, and efficacy of tocilizumab in patients with noninfectious uveitis. Am J Ophthalmol 2017;183:71–80.

85. Heissiggerová J, Callanan D, de Smet MD, Srivastava SK, Karkanová M, Garcia-García O, et al. Efficacy and safety of sarilumab for the treatment of posterior segment noninfectious uveitis (SARIL-NIU): the phase 2 SATURN Study. Ophthalmology 2019;126:428–437.

86. Fleischmann R, Genoves MC, Lin Y, St John G, van der Heijde D, Wang S, et al. Long-term safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years’ follow-up. Rheumatology 2020;59:292–302.

87. Dick AD, Tugal-Tutkun I, Foster S, Zierhut M, Melissa Liew SH, Bezyakov V, et al. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. Ophthalmology 2013;120:777–787.

88. Deodhar A, Mease PJ, McInnes IB, Baraliakos X, Reich K, Blauvelt A, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. Arthritis Res Ther 2019;21:111.

89. Langley RG, Lebwohl M, Krueger GG, Szapary PO, Wasfi Y, Chan D, et al. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. Br J Dermatol 2015;172:1371–1383.

90. Mugheddu C, Atzori L, Del Piano M, Lappi A, Murgia S, et al. Successful ustekinumab treatment of noninfectious uveitis and concomitant severe psoriatic arthritis and plaque psoriasis. Dermatol Ther 2017;30.

91. Chateau T, Angioi K, Peyrin-Biroulet L. Two cases of successful ustekinumab treatment for non-infectious uveitis associated with Crohn's disease. J Crohns Colitis 2020;14:571.

92. Lasave AF, You C, Ma L, Abusamra K, Lamba N, Valdes Navarro M, et al. Long-term outcomes of rituximab therapy in patients with noninfectious posterior uveitis refractory to conventional immunosuppressive therapy. Retina 2018;38:395–402.

93. Miserochçi E, Modorati G, Berchicci L, Pontikaki I, Meroni P, Gerloni V. Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis. Br J Ophthalmol 2016;100:782–786.

94. Ahmed A, Foster CS. Cyclophosphamide or rituximab treatment of scleritis and uveitis for patients with granulomatosis with polyangiitis. Ophthalmic Res 2019;61:44–50.

95. Umran RMR, Shukur ZYH. Rituximab for sight-threatening refractory pediatric Vogt-Koyanagi-Harada disease. Mod Rheumatol 2018;28:197–199.

96. Davatchi F, Shams H, Rezaipoor M, Sadeghi-Abdollahi B, Shahram F, Nadji A, et al. Rituximab in intractable ocular
lesions of Behcet's disease; randomized single-blind control study (pilot study). *Int J Rheum Dis* 2010;13:246–252.

97. Sadreddini S, Noshad H, Molaeefard M, Noshad R. Treatment of retinal vasculitis in Behcet's disease with rituximab. *Mod Rheumatol* 2008;18:306–308.

98. Heiliggenhaus A, Misericocchi E, Heinz C, Gerloni V, Kotaniemi K. Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). *Rheumatology* 2011;50:1390–1394.

99. Cao JH, Oray M, Cocho L, Foster CS. Rituximab in the treatment of refractory noninfectious scleritis. *Am J Ophthalmol* 2016;164:22–28.

100. Iaccheri B, Androudi S, Bocci EB, Gerli R, Cagini C, Fiore T. Rituximab treatment for persistent scleritis associated with rheumatoid arthritis. *Ocul Immunol Inflamm* 2010;18:223–225.

101. Ahmadi-Simab K, Lamprecht P, Nölle B, Ai M, Gross WL. Successful treatment of refractory anterior scleritis in primary Sjogren's syndrome with rituximab. *Ann Rheum Dis* 2005;64:1087–1088.

102. Ahmed A, Foster CS. Cyclophosphamide or rituximab treatment of scleritis and uveitis for patients with granulomatosis with polyangiitis. *Ophthalmic Res* 2019;61:44–50.

103. Taylor SR, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. *Arthritis Rheum* 2009;60:1540–1547.

104. Joshi L, Lightman SL, Salama AD, Shirodkar AL, Pusey CD, Taylor SR. Rituximab in refractory ophthalmic Wegener's granulomatosis: PR3 titers may predict relapse, but repeat treatment can be effective. *Ophthalmology* 2011;118:2498–2503.

105. Cheung CM, Murray PI, Savage CO. Successful treatment of Wegener's granulomatosis associated scleritis with rituximab. *Br J Ophthalmol* 2005;89:1542.

106. Oral S, Kazokoglu H, Koc A, Yavuz S. Rituximab for remission induction in a patient with relapsing necrotizing scleritis associated with limited Wegener's granulomatosis. *Ocul Immunol Inflamm* 2008;16:230–232.

107. Umran RMR, Shukur ZYH. Rituximab for sight-threatening refractory pediatric Vogt-Koyanagi-Harada disease. *Mod Rheumatol* 2018;28:197–199.

108. Monferrer-Adsua C, Remoli-Sargues L, Hernández-Bel L, Gracia-Garcia A, Hernández-Garfella ML, Cervera-Taulet E. Rituximab in the treatment of Susac's syndrome: report of a case. *Eur J Ophthalmol* 2021;31:NP48–NP52.

109. Misericocchi E, Modorati G. Rituximab for noninfectious uveitis. *Dev Ophthalmol* 2012;51:98–109.

110. Tomkins-Netzer O, Taylor SR, Lightman S. Can rituximab induce long-term disease remission in patients with intraocular non-infectious inflammation? *Ophthalmologica* 2013;230:109–115.

111. Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Shergy W, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase IIb, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:2263–2271.

112. Tappeiner C, Misericocchi E, Bodaghi B, Kotaniemi K, Mackensen F, Gerloni V, et al. Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2015;42:706–711.

113. Galstian L, Zhobloubova E. SAT0510 abatacept in the treatment of juvenile idiopathic arthritis associated with uveitis. *Ann Rheum Dis* 2015;74:845.

114. Zulian F, Baizarin M, Falcini F, Martini G, Alessio M, Cimaz R, et al. Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis. *Arthritis Care Res* 2010;62:821–825.

115. Biolo C, Zannin ME, Arsenyeva S, Cimaz R, Misericocchi E, Dubko M, et al. Comparable efficacy of abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis. *J Rheumatol* 2016;43:2068–2073.

116. Curtis JR, Yang S, Patkar NM, Chen L, Singh JA, Cannon GW, et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. *Arthritis Care Res* 2014;66:990–997.

117. Blair HA, Deeks ED. Abatacept: a review in rheumatoid arthritis. *Drugs* 2017;77:1221–1233.

118. Plskova J, Greiner K, Forrester JV. Interferon-alpha as an effective treatment for noninfectious posterior uveitis and panuveitis. *Am J Ophthalmol* 2007;144:55–61.

119. Eser-Ozturk H, Sulu Y. The results of interferon-alpha treatment in Behcet uveitis. *Ocul Immunol Inflamm* 2020;28:498–504.

120. Lee JH, Lee CS, Lee SC. Interferon alpha-2a treatment for refractory Behcet uveitis in Korean patients. *BMC Ophthalmol* 2018;18:52.

121. Kötter I, Zierhut M, Eckstein AK, Vonthrin R, Ness T, Günaydın I, et al. Human recombinant interferon alfa-2a for the treatment of Behcet's disease with sight threatening posterior or panuveitis. *Br J Ophthalmol* 2003;87:423–431.

122. Guillaume-Czitrom S, Berger C, Pajot C, Bodaghi B, Wechsler B, Kone-Paut I. Efficacy and safety of interferon-α treatment in the corticoiddependent uveitis of paediatric Behcet's disease. *Rheumatology* 2007;46:1570–1573.

123. Sobaci G, Erdem U, Durukan AH, Erdurman C, Bayer A, Köksal S, et al. Safety and effectiveness of interferon alpha-2a in the treatment of patients with Behcet's uveitis refractory to conventional treatments. *Ophthalmology* 2010;117:1430–1435.

124. Bodaghi B, Gendron G, Wechsler B, Terrada C, Cassoux N, Thi Huong DL, et al. Efficacy of interferon alpha in the treatment of refractory and sight threatening uveits: a retrospective monocentric study of 45 patients. *Br J Ophthalmol* 2007;91:335–339.

125. Deuter CM, Zierhut M, Möhle A, Vonthrin R, Stöbiger N, Kötter I. Long-term remission after cessation of interferon-α treatment in patients with severe uveitis due to Behçet's disease. *Arthritis Rheum* 2010;62:2796–2805.

126. De Simone L, Sangiovanni A, Aldieri R, Mastrofilippo V, Bolletta E, Invernizzi A, et al. Interferon alpha-2a treatment for post-uveitic refractory macular edema. *Ocul Immunol Inflamm* 2020;28:322–328.

127. Deuter CM, Doycheva D, Koetter I, Zierhut M. Long-term results of treatment with interferon alpha for chronic
uveitic cystoid macular edema. Invest Ophthalmo Vis Sci 2012;53:4262.

128. Oray M, Onal S, Uludag G, Akbay AK, Tugal-Tutkun I. Interferon alpha for the treatment of cystoid macular edema associated with presumed ocular tuberculosis. J Ocul Pharmacol Ther 2017;33:304–312.

129. Invernizzi A, Iannaccone F, Marchi S, Mastrofilippo V, Coassin M, Fontana L, et al. Interferon alpha-2a for the treatment of post-infectious uveitis secondary to presumed intraocular tuberculosis. Ocul Immunol Inflamm 2019;27:643–650.

130. Mackensen F, Jakob E, Springer C, Dobner BC, Wiehler U, Weimer P, et al. Interferon versus methotrexate in intermediate uveitis with macular edema: results of a randomized controlled clinical trial. Am J Ophthalmol 2015;165:478–486.e1.

131. Sleijfer S, Bannink M, Van Gool AR, Kruit WH, Stoter G. Side effects of interferon-alpha therapy. Pharm World Sci 2005;27:423–431.

132. Paley MA, Karacal H, Rao PK, Margolis TP, Miner JJ. Tofacitinib for refractory uveitis and scleritis. Am J Ophthalmal Case Rep 2018;13:53–55.

133. Bauermann P, Heiligenhaus A, Heinz C. Effect of janus kinase inhibitor treatment on anterior uveitis and associated macular edema in an adult patient with juvenile idiopathic arthritis. Ocul Immunol Inflamm 2019;27:1232–1234.

134. Miserochi E, Giuffré C, Cornalba M, Pontikaki I, Cimaz R. JAK inhibitors in refractory idiopathic juvenile arthritis-associated uveitis. Clin Rheumatol 2020;39:847–851.

135. Wollenhaupt J, Lee EB, Curtis JR, Silverfield J, Terry K, Soma K, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatomatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther 2019;21:89.

136. Yamanuha J, Albini T. Current and new steroid therapy in noninfectious uveitis. Retina Specialist [Internet]. 2019. Available from: https://www.retina-specialist.com/article/current-and-new-steroid-therapy-in-noninfectious-uveitis/

137. Thorne JE, Sugar EA, Holbrook JT, et al. Periocular triamcinolone vs. intravitreal triamcinolone vs. intravitreal dexamethasone implant for the treatment of uveitic macular edema: the PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) trial. Ophthalmology 2019;126:283–295.

138. Lowder C, Belfort R, Lightman S, Foster CS, Robinson MR, Schiffman RM, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Arch Ophthalmol 2011;129:545–553.

139. Moissieiev E, Goldstein M, Waisbourd M, Barak A, Loewenstein A. Long-term evaluation of patients treated with dexamethasone intravitreal implant for macular edema due to retinal vein occlusion. Eye 2013;27:65–71.

140. Jaffe GJ, Foster CS, Pavesio CE, Paggiarino DA, Riedel GE. Effect of an injectable fluocinolone acetonide insert on recurrence rates in chronic noninfectious uveitis affecting the posterior segment: twelve-month results. Ophthalmology 2019;126:601–610.

141. Jaffe GJ, Pavesio CE, Study Investigators. Effect of a fluocinolone acetonide insert on recurrence rates in noninfectious intermediate, posterior, or panuveitis: three-year results. Ophthalmology 2020;127:1395–1404.

142. Multicenter Uveitis Steroid Treatment Trial Research Group, Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Sugar EA. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. Am J Ophthalmol 2010;149:550–561.e10.

143. Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group. Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. JAMA 2017;317:1993–2005.

144. Emami-Naeini P, Yiu M. Medical and surgical applications for the suprachoroidal space. Int Ophthalmol Clin 2019;59:195–207.

145. Henry CR, Shah M, Barakat MR, Dayani P, Wang RC, Khurana RN, et al. Suprachoroidal CLS-TA for non-infectious uveitis: an open-label, safety trial (AZALEA). Br J Ophthalmol 2021;bjophthalmol-2020-318019.

146. Yeh S, Khurana RN, Shah M, Henry CR, Wang RC, Kissner JM, et al. Efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: phase 3 randomized trial. Ophthalmology 2020;127:948–955.

147. Conradi CD, Yeh S. A review of ocular drug delivery platforms and drugs for infectious and noninfectious uveitis: the past, present, and future. Pharmaceutics 2021;13:1224.

148. Taylor SR, Banker A, Schlaen A, Couto C, Matthe E, Joshi L, et al. Intraocular methotrexate can induce extended remission in some patients in noninfectious uveitis. Retina 2013;33:2149–2154.

149. Taylor SR, Habot-Wilner Z, Pacheco P, Lightman SL. Intraocular methotrexate in the treatment of uveitis and uveitic cystoid macular edema. Ophthalmology 2009;116:797–801.

150. Macular Edema Ranibizumab v. Intravitreal Anti-Inflammatory Therapy Trial (MERIT) (2017). Clinicaltrial.gov identifier: NCT02623426. Available from: https://clinicaltrials.gov/ct2/show/NCT02623426?cond=Macular+Oedema+Ranibizumab+v.+Intravitreal+anti-inflammatory+Therapy+Trial&draw=2&rank=1

151. Frenkel S, Hendler K, Siegal T, Shalom E, Pe'er J. Intraocular methotrexate for treating vitreoretinal lymphoma: 10 years of experience. Br J Ophthalmol 2008;92:383–388.

152. Merrill PT, Clark WL, Banker AS, Fardeau C, Franco P, LeHoang P, et al. Efficacy and safety of intravitreal sirolimus for noninfectious uveitis of the posterior segment: results from the Sirolimus Study Assessing anti-Inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. JAMA 2017;317:1993–2005.

153. Vigil EM, Sepah YJ, Watters AL, Sadiq MA, Ansari M, Bittencourt MG, et al. Assessment of changes in quality of life among patients in the SAVE Study – sirolimus as therapeutic approach to uVEitis: a randomized study to assess the safety and bioactivity of intravitreal and subconjunctival injections of sirolimus in patients with noninfectious uveitis. J Ophthalmic Inflamm Infect 2015;5:13.

154. Ibrahim MA, Sepah YJ, Watters A, Bittencourt M, Vigil EM, Do DV, et al. One-year outcomes of the SAVE study:
sirolimus as a therapeutic approach for UVEitis. *Transl Vis Sci Technol* 2015;4:4.

155. Nguyen QD, Sadiq MA, Soliman MK, Agarwal A, Do DV, Sepah YJ. The effect of different dosing schedules of intravitreal sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, in the treatment of non-infectious uveitis (an American ophthalmological society thesis). *Trans Am Ophthalmol Soc* 2016;114:T3.

156. Hamza MM, Macky TA, Sidky MK, Ragab G, Soliman MM. Intravitreal infliximab in refractory uveitis in Behcet’s disease: a safety and efficacy clinical study. *Retina* 2016;36:2399–2408.

157. Giganti M, Beer PM, Lemanski N, Hartman C, Schartman J, Falk N. Adverse events after intravitreal infliximab (Remicade). *Retina* 2010;30:71–80.

158. Giansanti F, Ramazzotti M, Vannozzi L, Rapizzi E, Fiore T, Iaccheri B, et al. A pilot study on ocular safety of intravitreal infliximab in a rabbit model. *Invest Ophthalmol Vis Sci* 2008;49:1151–1156.

159. Theodossiadis PG, Liarakos VS, Sfikakis PP, Charonis A, Agrogiannis G, Kavantzas N, et al. Intravitreal administration of the anti-TNF monoclonal antibody infliximab in the rabbit. *Graefes Arch Clin Exp Ophthalmol* 2009;247:273–281.

160. Kheir WJ, Mehanna CJ, Abdul Fattah M, Al Ghadban S, El Sabban M, Mansour AM, et al. Intravitreal adalimumab for the control of breakthrough intraocular inflammation. *Ocul Immunol Inflamm* 2018;26:1206–1211.

161. Hamam RN, Barikian AW, Antonios RS, Abdulaa MR, Alameddie RM, El Mollayess G, et al. Intravitreal adalimumab in active noninfectious uveitis: a pilot study. *Ocul Immunol Inflamm* 2016;24:319–326.

162. Sobolewska B, Chee SP, Zagui A, Goldstein DA, Smith JR, Fend F, et al. Vitreoretinal lymphoma. *Cancers* 2021;13:3921.

163. Hashida N, Ohguro N, Nishida K. Efficacy and complications of intravitreal rituximab injection for treating primary vitreoretinal lymphoma. *Transl Vis Sci Technol* 2012;11.

164. Eyevensys. Plasmid-based uveitis therapy proceeding to phase I trial [Internet]. San Francisco, CA: American Academy of Ophthalmology; 2017. Available from: https://www.aao.org/headline/plasmid-based-uveitis-therapy-proceeding-to-phase-

165. Buggage R, Behar-Cohen FF. EYS606 for the treatment of chronic non-infectious uveitis (NIU): results from part 1 of a first-in-human (EYS606-CT1) study. *Invest Ophthalmol Vis Sci* 2020;61:3170.

166. Businesswire. Eyevensys presents initial data from phase I/II trial of innovative, non-viral gene therapy for ocular diseases at 11th annual ophthalmology innovation summit [Internet]. Businesswire; 2019. Available from: https://www.businesswire.com/news/home/2019101005298/en/Eyevensys-Presents-Initial-Data-from-Phase-III-Trial-of-Innovative-Non-Viral-Gene-Therapy-for-Ocular-Diseases-at-11th-Annual-Ophthalmology-Innovation-Summit

167. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol* 2005;140:509–516.

168. Jabs DA. Immunosuppression for the uveitides. *Ophthalmology* 2018;125:193–202.