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Biologic Drugs for the Treatment of Noninfectious Uveitis

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Abstract: The management of noninfectious uveitis is constantly evolving. A new "biologic era" in treatment began after the effectiveness of tumor necrosis factor-alpha blocking drugs was demonstrated in rheumatologic inflammatory diseases. The goal of specific immunomodulation with a biologic drug is to target inflammation at the molecular level with a low rate of serious adverse events. The purpose of this review is to summarize current knowledge of biologic drugs in the treatment of noninfectious uveitis by describing clinical studies and recent pharmacological developments.

Key Words: biologic, drug, immunomodulation, uveitis

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Uveitis—the broad term for intraocular inflammation—is one of the chief causes of legal blindness in the Western world, where noninfectious forms of uveitis (NIU) prevail.[1] Although identification of causes and investigation of basic mechanisms continue, a therapeutic arsenal is available to reduce inflammation and prevent vision loss. Corticosteroids are usually the first drugs used to treat NIU, but their long-term use is limited due to a myriad of side effects. Immunomodulatory therapy is implemented when intraocular inflammation is not successfully controlled by systemic prednisone dosed at $\leq$5 mg/d beyond 3 months, if the corticosteroid is not tolerated and/or in severe sight-threatening NIU.[2,3]

Immunomodulatory therapy is divided into conventional immunomodulatory drugs and biologic response modifying drugs, which are commonly referred to as "biologics." When conventional immunomodulatory drugs are not effective in controlling inflammation at maximum tolerable doses, biologics are the next step as treatment is escalated.[4]

Biologic response modifiers are a category of immunomodulatory drugs that target inflammatory molecules, such as cytokines. They are used in place of, or concomitant with, other immunomodulatory drugs. Infliximab and adalimumab, both anti-tumor necrosis factor (TNF)-α antibody-based drugs, are the most commonly prescribed biologics in patients with NIU. A large number of biologics have been developed, and in theory, modulating inflammation specifically should be highly effective and avoid the adverse reactions that occur with conventional immunomodulatory drugs or corticosteroids.

An extensive clinical evaluation is required before the initiation of any immunomodulatory drug. Baseline blood cell count, and liver enzyme and creatinine tests should be performed, as well as an assessment of cardiovascular and endocrinological status, review of immunization record, and consideration of possible latent infections, such as tuberculosis and hepatitis B or C virus disease.[5] If there is a previous history of neoplasm, patients must be closely monitored for recurrence. Yates et al[6] reported an increased risk of malignancy—mainly nonmelanoma skin cancer and non-Hodgkin lymphoma—in the patients with NIU who were treated with immunomodulatory therapy. Long-term follow-up of the Systemic Immunosuppressive Therapy for Eye Diseases cohort showed no increased overall and risk-related cancer mortality for the most frequently used immunomodulatory drugs, including anti-TNF-α agents.[7]

The treatment of uveitis with biologics generally requires a multidisciplinary approach, with co-management by rheumatologists and other medical specialists. Children are typically co-managed with a pediatrician. Table 1 summarizes the biologic drugs used to treat uveitis, including doses and side effects.

ANTITUMOR NECROSIS FACTOR-α

TNF-α is a master cytokine in the inflammatory process, being synthesized by most immune cells, and many nonimmune cells.[8] Soluble and transmembrane TNF-α are the active forms that bind to 2 TNF-α receptors (TNFR): TNFR1 (p55), which is widely expressed throughout the body, and TNFR2 (p75), which is more restricted to the immune system.

Adverse drug reactions attributed to TNF-α blockers as a group include infections (mycobacterial, bacterial, viral, and fungal), neutropenia, autoimmunity (asymptomatic autoantibodies or drug-induced lupus), malignancy, demyelinating disease, heart failure, and injection or infusion reactions.[9] Brain magnetic resonance is indicated to screen for demyelination in patients with intermediate uveitis before the commencement of TNF-α inhibitors.[5] Data from large cohorts of patients with inflammatory bowel disease using anti-TNF-α agents found no increase in the rates of malignancies.[10,11]

Infliximab

Infliximab (Remicade, Janssen Biothec, Horsham, PA) is a chimeric anti-TNF-α monoclonal antibody, 75% constituted by a constant human portion and 25% by a variable murine portion,

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TABLE 1. Biologic Response Modifiers, Composition, Doses, and Adverse Reactions

Category	Drug	Composition	Adult Dose*	Adverse Reactions
Anti-TNFα	Infliximab	Chimeric monoclonal Ab	5–10 mg/kg IV in wk 0, 2, and 6, then every 4–8 wk	Infections, tuberculosis reactivation, rash, lupus-like illness, vascular thrombosis, demyelinating disease, congestive heart failure, abnormal liver function tests, malignancy
	Adalimumab	Human monoclonal Ab	40 mg SC every 2 wk	
	Golimumab	Human monoclonal Ab	50 mg SC every 4 wk SC or 2 mg/kg IV every 4 wk twice, then every 8 wk	
	Certolizumab	Pegylated recombinant humanized Fab monoclonal Ab fragment	400 mg/wk SC	
Anti-IL-1β	Anakinra	Recombinant receptor antagonist	100 mg/d SC	GI symptoms, hepatitis, infections, hypersensitivity reactions, renal toxicity
	Canakinumab	Human monoclonal Ab	From 150 mg SC every 8 wk to 300 mg every 4 wk	
Anti-IL-2	Daclizumab	Humanized receptor monoclonal Ab	1 mg/kg IV every 2 wk to every 4 wk or 2 mg/kg IV on day 1, repeating on day 14 or 2 mg/kg SC every 4 wk	GI symptoms, rash, infections, depression, alopecia, leukopenia, abnormal liver function tests, flu-like symptoms, immune-mediated disorders
Anti-IL-6	Tocilizumab	Humanized receptor monoclonal Ab	4 mg/kg or 8 mg/kg IV every 4 wk or 162 mg/wk SC	GI symptoms, infections, abnormal liver function tests, hyperlipidemia, systemic hypertension, myelosuppression, pancreatitis, anaphylaxis
	Sarilumab	Human receptor monoclonal Ab	200 mg SC every 2 wk	
Anti-IL-17A	Secukinumab	Human monoclonal Ab	30 mg/kg IV every 4 wk	GI symptoms, infections, urinary symptoms, fever, anorexia, urticaria
Anti-IL-12/ IL-23	Ustekinumab	Human monoclonal Ab	45 mg SC every 4 wk, followed by every 8 wk, then every 12 wk	GI symptoms, infusions reactions, infections, skin rashes, headaches, flu-like symptoms
Anti-CD20	Rituximab	Chimeric Ab	1000 mg/d IV on days 1 and 15, repeated after 6 mo or 375 mg/m^2 body surface/wk for 8 wk and then monthly for 4 mo	Infusion reactions, GI symptoms, infections, abnormal liver function tests, myelosuppression, progressive multifocal leukoencephalopathy
Selective co-stimulator modulator	Abatacept	Recombinant fusion protein	125 mg SC or 10 mg/kg IV at wk 0, 2, and 4; then every 4 wk	GI symptoms, infections, night sweats, flu-like symptoms, urinary symptoms, skin rashes
Interferons	IFN α-2a	Recombinant IFN	3–6 MIU SC or IM daily to 3 times/wk	GI symptoms, alopecia, abnormal thyroid function, infections, depression, myelosuppression, abnormal liver function tests
	IFN α-2b	Recombinant IFN	3–4.5 MIU/d SC for 2 wk, tapering to 3×/wk	
	IFN β	Recombinant IFN	44 μg SC 3×/wk	
Janus kinase inhibitors	Tofacitinib	JAK1 and JAK3 inhibitor	10 mg/d PO	GI symptoms, infections, anemia, systemic hypertension, thromboembolism, abnormal liver function tests
	Baricitinib	JAK1 and JAK2 inhibitor	4 mg/d PO	
Other	Intravenous immunoglobulin	Polyspecific IgG	1.5–2.5 g/kg IV across 3 days, repeated at variable intervals	Eczema, fever, systemic hypertension, thrombosis

Ab indicates antibody; GI, gastrointestinal; IFN, interferon; IL, interleukin; IV, intravenous; JAK, janus kinase; mo, months; MIU, million international units; PO, oral administration; SC, subcutaneous; TNF, tumor necrosis factor; wk, week(s).

*Pediatric doses are determined by the treating pediatrician, depending on weight and other medical considerations.

that binds to both soluble and transmembrane TNF-α. Infliximab also induces regulatory T-cells in the peripheral blood of patients with Behçet uveitis.[12] It is usually administered at a dose of 5 mg/kg as an intravenous infusion given in weeks 0, 2, and 6, followed by a maintenance dose every 4 to 8 weeks. Infliximab is effective in the treatment of NIU unresponsive to other drugs, including adalimumab.[13–16] It has a long history of use in the treatment of Behçet disease, and has also been studied in Vogt-Koyanagi-Harada (VKH) syndrome, birdshot retinochoroidopathy, sarcoid uveitis, juvenile idiopathic arthritis (JIA)-associated uveitis, HLA-B27-associated anterior uveitis and undifferentiated uveitis, with approximately 82% of patients achieving clinical remission in a median time of 127 days.[17,18] A prospective study with patients with aggressive NIU identified a 60% retention rate for infliximab at 2 years of treatment.[19] Even when used in combination with other immunomodulatory agents, infliximab is well tolerated.[20] Intravitreal use of infliximab generated controversy initially,[21] but one recent study that evaluated this treatment at a dose of 1 mg/0.05 mL showed control of ocular inflammation and an acceptable safety profile in 20 patients with refractory Behçet uveitis across 18 weeks of follow-up.[22] There is a report of worsening of uveitis, with reduction in electroretinographic parameters, and deterioration in microperimetry, after treatment with intravitreal infliximab in a prospective open-label study.[23]

Adalimumab

Adalimumab (Humira, AbbVie Inc., North Chicago, IL) is a human monoclonal antibody that blocks soluble and transmembrane TNF-α.[24] Administered through subcutaneous injections, adalimumab is used at 40 mg every 2 weeks, with the possibility of shortening the administration interval if necessary.[25] The SYCAMORE study investigators prescribed a dose of 20 mg every 2 weeks in children weighing <30 kg and adult doses in children weighing >30 kg.[26] Inflammation control by adalimumab was found to be similar to infliximab in the treatment of NIU.[27,28] A prospective study compared the efficacy of infliximab versus adalimumab in refractory JIA-associated uveitis, with clinical remission over 24 months reported in 44.8% for infliximab and 60% for adalimumab.[29] In a prospective case series of 26 patients with sarcoid uveitis followed for 12 months, 22 of 26 patients were treated successfully with adalimumab.[30]

Adalimumab was approved by the US Food and Drug Administration for the treatment of NIU on the basis of 2 phase-3, randomized, double-masked placebo-controlled trials (VISUAL I and VISUAL II) conducted in 22 countries; these studies showed the drug's effectiveness in delaying time to treatment failure in patients with active (VISUAL I) and inactive (VISUAL II) NIU.[31,32] In VISUAL I, time to treatment failure was 24 weeks and 13 weeks for the patients treated with adalimumab and placebo, respectively. After 18 months, the adalimumab group had a 50% reduction in the risk of treatment failure compared to placebo. In VISUAL II, time to treatment failure for the adalimumab group was 18 months, compared with 8.3 months for the placebo group, with a 43% risk reduction of treatment failure at 18 months for adalimumab-treated patients. VISUAL III was an open-label extension study that assessed safety and efficacy of adalimumab in patients from VISUAL I and II studies with and without treatment failure with a follow-up of 78 weeks.[33] Among the 242 patients who entered the VISUAL III study with active NIU, 60% achieved control of the ocular inflammation at 12 weeks, and 66% had discontinued corticosteroids. Seventy-five percent of the 129 patients with inactive NIU at study entry were quiescent at 78 weeks, and 93% of the responders were corticosteroid-free. Drug discontinuation secondary to adverse reactions was described in 13% of cases (48/371), and lack or loss of efficacy in 6% of cases (22/371) at 78 weeks.

The SYCAMORE study addressed pediatric uveitis specifically. This was a multicenter, double-masked, clinical trial that randomized children and adolescents receiving methotrexate for active JIA-associated uveitis to treatment with methotrexate alone or concomitant with adalimumab.[26] Treatment failure occurred in 60% in the methotrexate-only group and 27% in the adalimumab group at 18 months of follow-up.[26] Long-term therapy seems to be necessary for sustained control, since a report from a 5-year follow-up from one of the SYCAMORE's centers showed that 92% of 28 patients had to resume treatment with adalimumab after its withdrawal.[34]

Intravitreal adalimumab was not effective for uveitic macular edema in a small study with 5 patients.[35] A retrospective study with 12 eyes of 7 patients showed inflammation control in 9 eyes at 26 weeks with 7 intravitreal injections per eye of adalimumab 1.5 mg/0.03 mL, but 1 eye had worsening of inflammation after the fourth injection.[36]

Adalimumab and infliximab display similar long-term retention rates, indicating that both drugs present comparable effectiveness and tolerability.[37] Adalimumab retention rate was 54% at 5 years of follow-up and was not influenced by concomitant use of other immunosuppressants, as determined by a retrospective cohort with 392 patients.[38] Reported discontinuation occurred due to inefficacy in 19% and adverse reactions in 9%.[38] Since infliximab is administered intravenously, it requires more visits to the clinic and thus may be more difficult for patients to integrate into their daily lives.

The development of antidrug antibodies may occur during treatment with adalimumab or infliximab therapy, decreasing their efficacy. Prescription of methotrexate or azathioprine concomitant with these anti-TNF-α drugs may address this issue.[39–41] A study showing a rate of 32% of anti-adalimumab antibodies found that, in only about half of patients, the antibodies were permanent and led to decreased bioavailability of adalimumab and worse outcomes.[42]

Golimumab

Golimumab (Simponi, Janssen Biotech, Horsham PA) is a human monoclonal antibody against soluble and transmembrane TNF-α.[43] Its route of administration may be either subcutaneous or intravenous. If prescribed subcutaneously, the usual dose is 50 mg every 4 weeks, whereas if administered intravenously, the recommended loading dose is 2 mg/kg every 4 weeks twice, extended to an 8-week interval. Golimumab was effective in the treatment of intraocular inflammation, especially in HLA-B27- and JIA-associated uveitis, but also in Behçet and undifferentiated NIU.[44–49] A retrospective study with 13 patients with refractory NIU showed resolution of intraocular inflammation in 12 of 13 patients at 6 months.[44] Another retrospective cohort of 17 patients with refractory JIA- and HLA-B27-associated uveitis reported that 12 individuals had inactive disease at last visit (mean follow-up of 22 months).[49]

Certolizumab

Certolizumab pegol (Cimzia, UCB, Inc., Smyrna, GA) is a humanized anti-TNF-α Fab monoclonal antibody fragment combined with polyethylene glycol.[50] Contrasting with other anti-TNF-α drugs, it does not have a fragment crystallizable (Fc) domain. These characteristics decrease immunogenicity and improve pharmacodynamics.[50] Certolizumab is administered at a dose of 400 mg/week subcutaneously. It has been evaluated in refractory Behçet uveitis, JIA-associated uveitis, and spondyloarthropathy-associated uveitis.[51] Incidence of uveitis flares was reduced in certolizumab-treated patients with axial spondyloarthropathy (3 per 100 patient-years) in comparison to placebo (10 per 100 patients-years) at 24 weeks of treatment, with those treated with certolizumab maintaining low incidence of uveitis flares until 96 weeks of follow-up.[52] Preliminary results of a multicenter prospective study that included 89 patients with spondyloarthropathy and recurrent anterior uveitis demonstrated an 87% decrease in risk of uveitis recurrence for the patients treated with certolizumab during a 48-week follow-up.[53]

Etanercept

Etanercept (Enbrel, Immunex Corporation, Thousand Oaks, CA) is a recombinant fusion protein, composed of the extracellular ligand-binding domain of the TNFR p75 linked to the Fc portion of human IgG1, that binds to soluble and transmembrane TNF-α.[54] It has been used extensively in the treatment of rheumatoid arthritis and the spondyloarthropathies. Nonetheless, it has proved to be ineffective in suppressing intraocular inflammation and may be associated with paradoxical uveitis—or just low effectiveness in preventing uveitis flares—and hence it is not used to treat NIU.[54–59]

ANTI-INTERLEUKIN-1 BETA

Interleukin (IL)-1β is a cytokine produced by many cell types, including mononuclear phagocytes, which are key innate immune cells. There are 2 forms of IL-1—IL-1α and IL-1β—which act through a common receptor that is naturally blocked by IL-1 receptor antagonist (IL-1RA).[60] IL-1β has pleiotropic actions during inflammation, including the activation of various cells involved in immune responses.

Adverse drug reactions attributed to IL-1β-targeted biologics include infections, local injection site reactions (diminishing with time), and hepatitis. Systemic JIA-associated lung disease does not have a clear causal relationship with the use of these agents.[61]

Anakinra and Canakinumab

Anakinra (Kineret, Swedish Orphan Biovitrum AB, Stockholm, Sweden) is a recombinant human IL-1 receptor antagonist. Administered daily at a subcutaneous dose of 100 mg, anakinra may be indicated in rheumatoid arthritis and cryopyrin-associated periodic syndromes.[60] Canakinumab (Ilaris, Novartis Pharmaceuticals, Basel, Switzerland) is a human anti-IL-1β monoclonal antibody. It is used in the treatment of cryopyrin-associated periodic syndromes, systemic JIA, TNFR-associated periodic syndrome, mevalonate kinase deficiency, and familial Mediterranean fever.[60] Subcutaneous doses range from 150 mg every 8 weeks to 300 mg every 4 weeks.[62]

Seven of 9 patients with refractory Behçet uveitis responded to treatment with anakinra in a case series.[63] Nineteen patients with Behçet disease experienced a reduction in the annual number of flares of uveitis from 200 to 49/100 patients/year after introduction of IL-1β antagonists (as monotherapy or given with another immunomodulatory drug).[62] Effectiveness of anakinra and canakinumab has been correlated with longer duration of Behçet disease and ocular involvement, with the group that presented a sustained response (over 52 weeks) achieving disease control by 3 months of therapy.[64] One patient with multiple sclerosis-associated uveitis and HLA-B27 positive achieved long-term resolution of inflammation after treatment with anakinra.[65] One case series of 2 children indicated therapeutic benefit for idiopathic uveitis and JIA-associated uveitis.[66]

Gevokizumab

Gevokizumab (XOMA 052, XOMA Corporation, Berkeley, CA) is a humanized anti-IL-1β monoclonal antibody, which is administered subcutaneously every 4 weeks at a dose of 60 mg.[67] Despite having fast and sustained anti-inflammatory activity in severe Behçet uveitis in a phase-2 study, results of phase-3 trials of gevokizumab did not meet end-points for effectiveness in uveitis.[67–69] Consequently, the drug has not been marketed for clinical practice.

ANTI-INTERLEUKIN-2

Daclizumab

Daclizumab (Zenapax, Genentech, Inc., South San Francisco, CA) is composed of 90% human and 10% murine antibody sequences against CD25, which is the alpha subunit of the IL-2 receptor. This drug selectively inhibits activation of T-cells. It also induces regulatory natural killer cells that produce IL-10.[70] It was first used to suppress acute rejection after solid organ transplantation, later being approved for relapsing forms of multiple sclerosis. Some retrospective and prospective pilot studies described safety and positive effects of daclizumab in patients with refractory NIU. Various dosage schemes were reported: 1 mg/kg intravenous every 2 weeks, extending the interval up to 4 weeks; high dose infusions of 2 mg/kg intravenous on day 1, repeating on day 14; and 2 mg/kg subcutaneously monthly. Adverse reactions include peptic disturbances, skin eruption, hepatotoxicity, leukopenia, and infections.[71–74]

A retrospective review of 39 patients with intermediate and posterior NIU treated with daclizumab (intravenous, subcutaneous and high-dose schemes) for a mean of 40 months showed improvement of >2 lines in visual acuity in 7 patients, and worsening by 2 lines in 6 patients. Four patients who were also on concomitant use of other immunomodulators developed neoplasms.[75]

ANTI-INTERLEUKIN-6

Tocilizumab

Tocilizumab (Actemra, Hoffmann-La Roche Ltd., Basel, Switzerland) is a humanized monoclonal antibody that binds to both soluble and transmembrane receptors of IL-6, a cytokine with several proinflammatory actions, such as increase in vascular permeability and induction of the Th17 cell population that participates in autoimmune inflammation.[76] It is an option for

rheumatoid arthritis refractory to ≥1 anti-TNF-α drugs, systemic and polyarticular JIA, and Castleman disease therapy.[77] Tocilizumab may be administered by intravenous infusions or subcutaneously. Intravenous doses are 4 mg/kg or 8 mg/kg every 4 weeks, and the subcutaneous dose is 162 mg weekly. A report of 4 patients with JIA, whose uveitis flared up when switching to subcutaneous drug, suggests that the subcutaneous route may be less effective than the intravenous.[78]

Reported adverse reactions of IL-6 receptor blockade include infusion reactions, gastrointestinal disturbances, changes in liver function tests, hyperlipidemia, neutropenia, thrombocytopenia, and infections.

Tocilizumab is effective in cases of Behçet disease, birdshot retinochoroidopathy, JIA-associated uveitis, sympathetic ophthalmia, ocular sarcoidosis, and idiopathic panuveitis refractory to both conventional immunomodulatory therapy and anti-TNF-α drugs or interferons (IFNs).[79–85] Preliminary 6-month results from the STOP-uveitis trial, which is evaluating the safety, tolerance, and bioactivity of tocilizumab in adults with NIU, indicate improvement in visual acuity by at least 2 lines in 30% of patients and a 2-step reduction in vitreous flare in 43%, plus improvement in macular edema if present.[84] Nonetheless, the APTITUDE trial, a phase-2 study that evaluated tocilizumab in 21 patients with JIA-associated uveitis refractory to anti-TNF-α therapy, demonstrated a drug efficacy of only 34% after 12 weeks of treatment, failing to meet the study's primary endpoint. At the same time, tocilizumab demonstrated a good safety profile and coexistent macular edema resolved in 3 of 4 patients[86].

Sarilumab

Sarilumab (KEVZARA, Regeneron Pharmaceuticals and Sanofi-Aventis US, Inc., Tarrytown, NY) is a human anti-IL-6 receptor monoclonal antibody, approved for rheumatoid arthritis therapy. Sarilumab was assessed by a randomized, phase-2 study, which reported a 2-step or greater reduction in vitreous haze and/or a decrease in corticosteroid dose in 64% of NIU patients taking sarilumab compared with 35% in the placebo group at 16 weeks of treatment. Sarilumab was used at a dose of 200 mg subcutaneously every 2 weeks for 16 weeks, which was well-tolerated.[87]

ANTI-INTERLEUKIN-17

Secukinumab

Secukinumab (Cosentyx, Novartis Pharmaceuticals, Basel, Switzerland) is a human anti-IL-17A monoclonal antibody used in the treatment of plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis, in both intravenous and subcutaneous formulations. A phase-2, multicenter, randomized, double-masked trial showed that intravenous secukinumab at a dose of 30 mg/kg every 4 weeks achieved a response in >72% of patients with NIU, and led to remission in over one-fourth of these individuals, with an acceptable safety profile.[88] Subcutaneous secukinumab at a dose of 300 mg had a 33.3% response rate. A previous trial using secukinumab administered only by the subcutaneous route did not show a decrease in NIU recurrences during discontinuation of immunomodulatory agents.[89] Clinicians using this drug should remain alert to infections, raised serum lipids, noninfectious pharyngitis, and gastrointestinal disturbances as side effects that may influence management decisions.[90]

ANTI-INTERLEUKIN-23

Ustekinumab

Ustekinumab (Stelara, Janssen Biotech Inc, Horsham, PA) is a monoclonal antibody against human IL-12/IL-23 p40 subunit that is effective for the treatment of plaque psoriasis, psoriatic arthritis, and inflammatory bowel disease. Interleukin-23 is an important cytokine for driving Th17 cell-related pathology.[91] The drug is administered via subcutaneous injections of 45 mg, repeated after 4 weeks and then at 8- to 12-week intervals, with an initial weight-based intravenous infusion in patients with inflammatory bowel disease. A few case reports have described ustekinumab for the treatment of NIU: 1 patient with psoriatic arthritis and psoriasis, and 2 patients with Crohn's disease, including 1 with multiple sclerosis.[92,93] A phase-2 trial (NCT02648581) is ongoing to evaluate ustekinumab efficacy in patients with Behçet uveitis. Development of antibodies against ustekinumab is not infrequent and may reduce efficacy. There are also increased risk of infections and gastrointestinal disturbance that require clinical monitoring.[94]

ANTI-CD20

Rituximab

Rituximab (Rituxan, Genentech Inc., San Francisco, CA) is a chimeric human and murine monoclonal antibody that targets CD20, a molecule expressed on the surface of circulating B-cells.[95] Intravenous administration schemes vary from 1000 mg/infusion on days 1 and 15, which may be repeated after 6 months depending on the activity of the NIU,[96,97] to 375 mg/m^2 body surface weekly during 8 weeks and then monthly for 4 subsequent months.[95,98] Rituximab has improved intraocular inflammation in individual cases and case series of refractory Behçet disease, VKH syndrome, retinal vasculitis, JIA-associated uveitis, HLA-B27-associated uveitis, intermediate uveitis, and undifferentiated panuveitis.[95–99] Approximately 45 months of follow-up of 8 patients with recalcitrant JIA-associated uveitis revealed that intraocular inflammation resolved in all after a mean of 9 infusions, whereas arthritis persisted in 2, and no serious adverse reactions were reported.[96] Uveitis recurrences have varied from around 22% to 57% of cases in different dosage schemes.[95,98] Adverse effects include infusion reactions, liver enzyme abnormalities, infections, myelosuppression, hypogammaglobulinemia, and progressive multifocal leukoencephalopathy.

SELECTIVE COSTIMULATION MODULATOR

Abatacept

Abatacept (Orencia, Bristol-Myers Squibb Company, New York, NY) is a recombinant fusion protein made of a human IgG1 fragment fused to the portion of cytotoxic T-lymphocyte-associated protein (CTLA)-4. The protein binds to CD80 or CD86 on antigen-presenting cells, inhibiting the costimulatory signal necessary for T-cell activation.[100] It is administered as a weekly 125 mg subcutaneous injection or by intravenous infusions at a dose of 10 mg/kg (up to a maximum of 750 mg) at 0, 2, and 4 weeks, and then every 4 weeks.[100]

Effectiveness of abatacept for recalcitrant NIU was observed in a case series of 7 patients with JIA-associated uveitis. However,

a retrospective cohort of 21 patients with refractory JIA-associated uveitis, who were receiving abatacept, documented residual uveitis in 10 patients, and although remission was achieved in 11 patients, intraocular inflammation subsequently recurred in 8 of them.[100,101] Roughly 55% of 35 patients with JIA-associated uveitis treated with abatacept as first-line or second-line therapy achieved remission in 12 months of treatment in a retrospective analysis.[102] Abatacept is generally well tolerated, and although not associated with large numbers of infections, deserves vigilance in patients receiving it.[103]

INTERFERONS

The IFN family of cytokines have extensive activities in immune responses.[104] They have been used therapeutically for a broad range of infectious and noninfectious inflammatory diseases, including NIU.

Interferon-α-2a

Recombinant IFN-α-2a is used in the treatment of chronic hepatitis C and various cancers, including chronic myeloid leukemia and Kaposi sarcoma.[105] There are quite varying dosing schedules, depending on considerations that include indication and whether the preparation is pegylated. Despite flu-like symptoms being commonly reported as adverse effects, IFN-α-2a is generally well tolerated, and severe adverse reactions are rare. Side effects include gastrointestinal disturbances, thyroid dysfunction, alopecia, fibromyalgia, depression, liver function test abnormalities, leukopenia, and thrombocytopenia.

Studies conducted in persistent Behçet uveitis have indicated effective control of inflammation in >80% of cases.[106–109] A retrospective analysis of 44 patients treated with IFN-α-2a revealed that 64% had a recurrence of uveitis and 20% maintained remission for up to 24 months.[110] A prospective cohort of 50 patients reported an overall response of 92% and an absence of relapses in 82% with a follow-up of 3 years.[111] Forty percent of patients had sustained remission after discontinuation of treatment for a mean of 29.5 months.

Use of IFN-α-2a for recalcitrant macular edema was assessed by Deuter et al[112] and De Simone et al.[113] When administered at a dose of 3 or 6 million international units subcutaneously per day initially, with subsequent tapering, the drug achieved response rates of 63% and 100%, respectively. One randomized controlled trial of IFN-α-2a versus corticosteroids versus no treatment for NIU-associated macular edema showed a significant reduction in the central foveal thickness at 4 months for IFN-α-2a and corticosteroids groups in a per protocol analysis.[114] Pegylated IFN-α-2a at a dose of 90 or 180 μg weekly was evaluated retrospectively in 7 patients with persistent uveitic macular edema, with improvement in all cases.[115] Recently, IFN-α-2a was used to treat macular edema secondary to intraocular tuberculosis in 6 patients.[116] Interestingly, in vitro studies using retinal pigment epithelial cells show that IFN-α-2a may enhance blood–retinal barrier function.[117]

Interferon-α-2b

The pegylated IFN-α-2a and IFN-α-2b appear to share the same pharmacokinetic properties.[118] Side effects of IFN-α-2b are similar to IFN-α-2a, but IFN-α-2a appears to be more immunogenic than the IFN α-2b in the treatment of chronic myeloid leukemia.[119] A case series of 4 patients with persistent Behçet uveitis indicated therapeutic effect of subcutaneous IFN-α-2b, using a loading dose of 3 to 4.5 million international units daily for 2 weeks, with tapering to 3 times weekly.[120] Both IFN-α-2a and IFN-α-2b were effective in a retrospective analysis of 35 patients with refractory uveitic macular edema.[121] Intravitreal IFN-α-2b administered as a single injection limits inflammation in experimental endotoxin-induced uveitis.[122]

Interferon-β

Recombinant IFN-β is approved for the treatment of multiple sclerosis and is used subcutaneously. However, oral administration of IFN-β strongly suppresses interphotoreceptor retinoid-binding protein-induced experimental autoimmune uveitis in rats.[123]

Some small studies have assessed the effectiveness of IFN-β for NIU. Becker et al[124] analyzed outcomes in 13 patients with multiple sclerosis and uveitis, showing reduction in macular edema and improvement in vision. A prospective randomized trial assessed IFN-β 44 μg 3 times weekly versus methotrexate 20 mg weekly in 19 patients with macular edema secondary to intermediate uveitis, and found significantly greater improvement in visual acuity in patients treated with IFN-β at 3 months.[125] Conversely, Jouve et al[126] described that patients with multiple sclerosis receiving IFN-β had more severe uveitis when compared with non-treated controls. Another small observational study in patients with multiple sclerosis using IFN-β or glatiramer acetate showed a reduction in episodes of ocular inflammation in both groups.[127] Side effects are diverse and include peripheral edema, gastrointestinal disturbances, elevated liver enzymes, neurological symptoms, development of neutralizing antibodies, injection site reactions, and flu-like symptoms.[128]

JANUS KINASES INHIBITORS

Janus kinases (JAKs) are enzymes linked to cytokine membrane receptors that are involved in intracellular signaling via signal transduction and activators of transcription molecules.[129] Inhibiting JAKs interrupts proinflammatory signaling via the JAK/signal transduction and activators of transcription pathway. Tofacitininb (Xeljanz, Pfizer, USA), a JAK1/JAK3-selective inhibitor, and baricitinib (Olumiant, Eli Lilly/Incyte), a JAK1/JAK2-selective inhibitor, are already used in the clinic for rheumatoid arthritis.[129] Just a few case reports have been reported on the use of these agents in NIU. Four patients with severe refractory JIA-associated uveitis, who were treated with tofacitinib or baricitinib, experienced improvement in intraocular inflammation, whereas arthritis improved in only one.[130] In another patient with severe JIA-associated uveitis, treatment with tofacitinib resolved macular edema and the articular inflammation.[131] Rash, gastrointestinal symptoms, and abnormal liver function are among the side-effects. Baricitinib and filgotinib (Gilead Sciences, Inc. & Galapagos NV—a JAK1 inhibitor) are under presently investigation for NIU in registered clinical trials (NCT04088409 and NCT03207815, respectively).

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin (IVIG) is a naturally occurring polyclonal human IgG produced from the plasma of donors. This

preparation acts through several mechanisms, such as modulation of the cytokine synthesis and secretion, inhibition of complement activation, suppression of autoantibodies, and interactions with major histocompatibility complex class 1 molecules and adhesion molecules.[132] As the formulation may include traces of IgA, its use in patients with IgA deficiency carries a possibility of an anaphylactic reaction and therefore is contraindicated.[132–134] IVIG is used in the treatment of immunodeficiencies and systemic inflammatory diseases. Positive results have been reported with the use of IVIG in Behçet uveitis,[135] birdshot retinochoroidopathy,[136] VKH syndrome,[137] and other forms of refractory NIU.[133] There is variation in doses and dosing intervals, but IVIG is often administered as cycles of 1.5 to 2.5 g/kg across 3 days, repeated at intervals that vary from 2 weeks to 2 months or longer.[133,134,138] Adverse reactions include fever, myalgia, headache, rashes, systemic hypertension, and thrombosis.[133–136,138,139] There are case reports of bilateral anterior uveitis[140] and unilateral vasculitis[141] after administration of IVIG.

CONCLUSIONS

Uveitis is a sight-threatening disease that poses a heavy burden on the quality of life of the affected individuals, who are mainly in the working-age group.[142] Treatment is based on a stepladder approach: corticosteroids, conventional immunomodulatory drugs, and biologic response modifying drugs.[4] There has been considerable progress in the treatment of NIU over the past 20 years. In particular, biologic drugs have revolutionized the treatment of sight-threatening autoimmune and autoinflammatory forms. As laboratory research continues to illuminate the mechanisms of intraocular inflammation, new biologic drugs are constantly entering the pipeline, and thus further developments in this field are anticipated within the coming decade.

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