

Targeting interleukin-6 for noninfectious uveitis

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Abstract: Interleukin-6 (IL-6) is a pleiotropic cytokine implicated in the pathogenesis of many immune-mediated disorders including several types of non-infectious uveitis. These uveitic conditions include Vogt-Koyanagi-Harada syndrome, uveitis associated with Behçet disease, and sarcoidosis. This review summarizes the role of IL-6 in immunity, highlighting its effect on Th17, Th1, and plasmablast differentiation. It reviews the downstream mediators activated in the process of IL-6 binding to its receptor complex. This review also summarizes the biologics targeting either IL-6 or the IL-6 receptor, including tocilizumab, sarilumab, sirukumab, olokizumab, clazakizumab, and siltuximab. The target, dosage, potential side effects, and potential uses of these biologics are summarized in this article based on the existing literature. In summary, anti-IL-6 therapy for non-infectious uveitis shows promise in terms of efficacy and side effect profile.

Keywords: interleukin-6, T lymphocyte, B lymphocyte, autoimmunity, uveitis

Role of interleukin-6 in immunity

Interleukin-6 (IL-6) is a pleiotropic cytokine produced by monocytes, macrophages, T-lymphocytes, and synovial fibroblasts, as well as other cell types. It is produced in response to damage-associated molecular patterns in injury, and pathogen-associated molecular patterns via toll-like receptor signaling in autoimmunity and infection (Figure 1). IL-6 has a wide variety of effects on different cell types throughout the body, including induction of acute-phase reactant production by hepatocytes, B-lymphocyte differentiation, and T-lymphocyte subset differentiation (Figure 1). Specifically, IL-6 plays a critical role in differentiation of CD4-positive T helper (Th) cells into Th17 cells which have been strongly implicated in the pathogenesis of immune-mediated diseases including noninfectious uveitis.^{1,2} IL-6 can also induce differentiation of CD8-positive cells into cytotoxic T-cells.^{2,3} IL-6 inhibits transforming growth factor β -mediated regulatory T-cell development, which is important in downregulating inflammatory responses.^{2,4} Additionally, IL-6 may be important in the pathogenesis of certain types of cancers, such as multiple myeloma.⁵

IL-6 signals in an autocrine and paracrine fashion by binding to the transmembrane cell surface IL-6 receptor as well as soluble IL-6 receptor.^{2,6} The IL-6 receptor includes the IL-6 binding domain (known as the IL-6 receptor) and the signal transduction chain, or gp130 (Figure 1A).⁷ Gp130 is common to other IL-6 family cytokines including interleukin-27 (IL-27), interleukin-35 (IL-35), interleukin-11 (IL-11), leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CTF1), and cardiotrophin-like cytokine (CLC).⁸

Activation of the IL-6 receptor requires a hexameric structure consisting of two molecules each of the IL-6 receptor, IL-6, and gp130.⁷ Activated gp130 results in activation of Janus kinase (JAK) and signal transducer and activator of transcription 3 (STAT3) pathways.^{2,6,8,9} SH2-domain containing tyrosine phosphatase-2 and mitogen activated protein kinases (MAPK) are also activated.⁸ IL-6 responsive genes include

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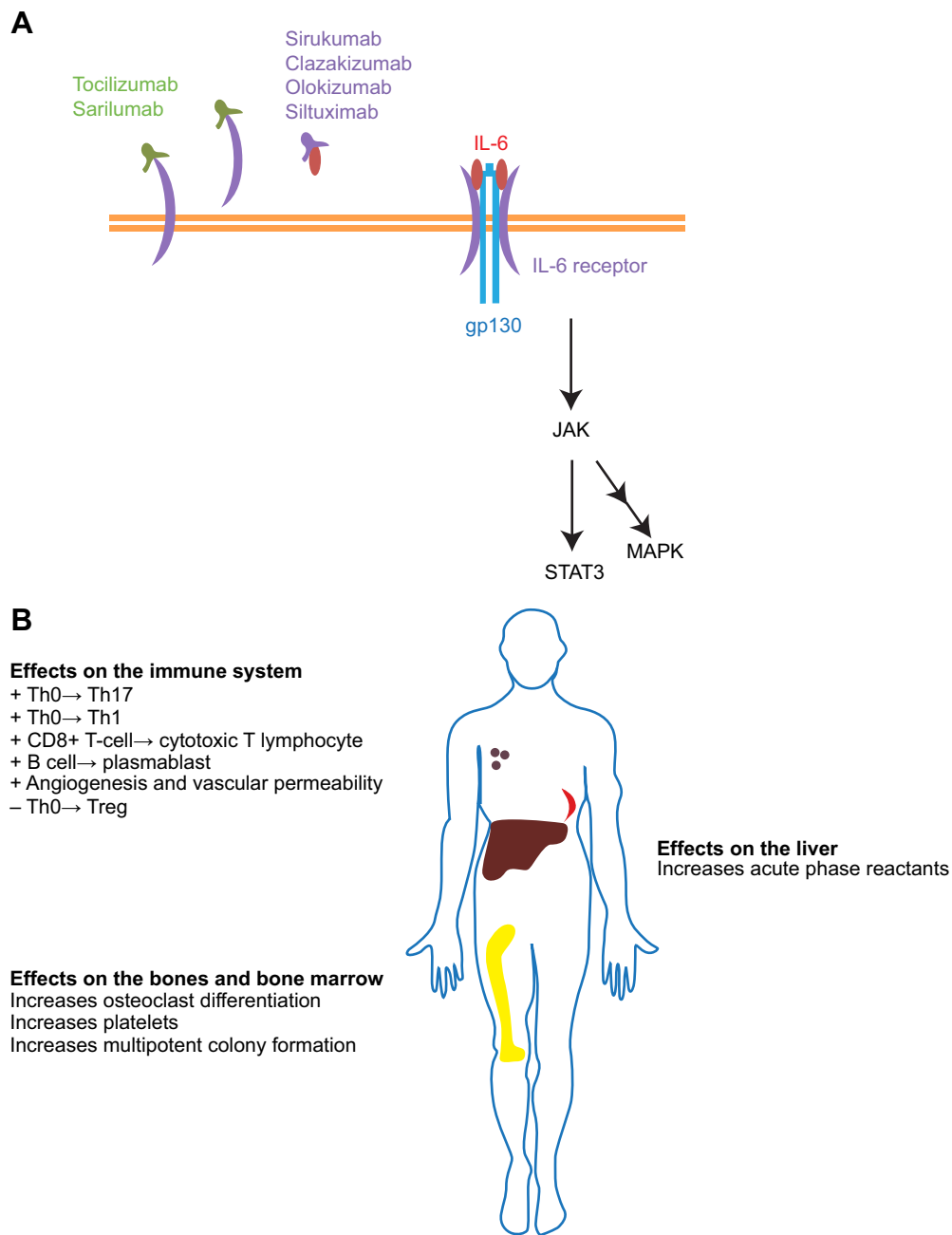


Figure 1 Signaling and activity of IL-6.

Notes: (A) Signaling of IL-6 occurs through its receptor and gp130 in a heterotrimeric complex. The targets of IL-6 biologics are also shown. (B) Biological activity of IL-6 in various human organ systems. Modified with permission of Elsevier from: A new era for the treatment of inflammatory autoimmune diseases by interleukin-6 blockade strategy, Tanaka et al; *Semin Immunol.* © 2014; 26(1).⁹ Permission conveyed through Copyright Clearance Centre, Inc.

Abbreviations: JAK, janus kinase; STAT3, signal transducer and activator of transcription 3; MAPK, mitogen activated protein kinase.

the acute phase reactants C-reactive protein, fibrinogen, and serum amyloid A.¹⁰ They also include hepcidin which blocks the action of ferroportin, an iron transporter in the gut, thus contributing to anemia of chronic inflammatory disease.¹¹ Importantly, IL-6 can induce production of vascular endothelial growth factor, resulting in the neovascular process that can sometimes accompany inflammation.¹²

The production of IL-6 is regulated by certain microRNAs such as miRNA-155, and proteins such as Regnase-1,

which negatively regulates IL-6 production by cells. Another regulator of IL-6 is the protein Arid5a (AT-rich interactive domain-containing protein 5a), which stabilizes IL-6 mRNA.¹³

Role of IL-6 in uveitis and other immune-mediated diseases

Both preclinical and clinical data support the importance of IL-6 in uveitis. Yoshimura et al¹⁴ demonstrated the

importance of IL-6 in an animal model of T-cell mediated uveitis, experimental autoimmune uveitis (EAU), by showing that treatment of EAU mice with an anti-IL-6 receptor antibody or, alternatively, EAU induction in IL-6-deficient mice results in dramatically reduced uveitic inflammation. This effect in EAU appears to occur via the suppression of both Th1 and Th17 differentiation, both of which are important in this animal model of uveitis.¹⁵ These same authors demonstrated elevated IL-6 concentrations in the vitreous fluid of chronic uveitis patients (with Vogt–Koyanagi–Harada syndrome, Behçet disease, sarcoidosis, and idiopathic uveitis), compared to nonuveitic patients (samples obtained from diabetic retinopathy, epiretinal membrane, and macular hole patients).¹⁴ Perez et al¹⁶ demonstrated that IL-6 was higher in the vitreous of patients with active intermediate or posterior uveitis compared to control patients. Even prior to the two above publications, however, Murray et al¹⁷ had demonstrated elevated aqueous humor levels of IL-6 in 24 patients with uveitis including in Fuchs' heterochromic iridocyclitis (n=16) and Toxoplasma uveitis (n=8). IL-6 levels are elevated in the serum of active uveitis patients as well.¹⁸

While rheumatoid arthritis (RA) is not commonly associated with uveitis, IL-6 production is dysregulated in the synovial fluid of RA patients.¹⁹ IL-6 and soluble IL-6 receptor are elevated in the serum of RA patients, and appear to correlate with disease activity.²⁰ Castleman disease, a condition resulting in lymphadenopathy, fever, night sweats, fatigue, and weight loss, is very rarely associated with uveitis.²¹ Oshitari et al²¹ showed that IL-6 aqueous levels were elevated in a patient with Castleman disease with anterior uveitis and retinal vasculitis resistant to oral steroid treatment but amenable to anti-IL-6 receptor antibody treatment. In juvenile idiopathic arthritis (JIA), serum IL-6 appears to be elevated in patients with active disease compared to inactive disease. It has been demonstrated that IL-6 levels decrease upon treatment in these patients.^{22,23} Table 1 summarizes the uveitic and systemic disorders associated with dysregulated IL-6 or IL-6 receptor (Table 1).

Targeting IL-6 for uveitis and systemic inflammatory disorders

Tocilizumab (Genentech, South San Francisco, CA, USA) is a monoclonal antibody against soluble and membrane-bound IL-6 receptor that is approved for the treatment of moderate to severe RA and JIA that has failed treatment with other disease modifying biologics. It has been used successfully in case reports in JIA uveitis refractory to prior TNF- α blockade,^{24,25} Castleman disease-associated uveitis, birdshot

Table 1 Conditions in which IL-6 plays a role in pathogenesis

Uveitic diseases ^{16–18,21,35}
Vogt–Koyanagi–Harada syndrome
Toxoplasma chorioretinitis
Fuchs heterochromic iridocyclitis
Behçet disease-associated uveitis
Sarcoidosis-associated uveitis
Idiopathic uveitis
Systemic inflammatory disorders ^{2,36–39}
Chronic rheumatoid arthritis
Juvenile idiopathic arthritis and Still disease
Castleman disease
Graves disease
Inflammatory bowel disease
Systemic sclerosis
Relapsing polychondritis
Ankylosing spondylitis
Infectious diseases ^{40–42}
HIV
HTLV-1
Cerebral malaria
Neoplastic diseases ^{43–46}
Breast cancer
Colon cancer
Prostate cancer
Multiple myeloma
Neurological diseases ^{47,48}
Alzheimers disease
Multiple sclerosis

Note: Modified from Interleukin-6 blockade in ocular inflammatory diseases. Mesquida M, et al; *Clin Exp Immunol*. 2014;176(3).¹⁵ © 2014 John Wiley and Sons Inc.
Abbreviation: HTLV-1, human T-lymphotropic virus-1.

chorioretinopathy, Behçet disease, and refractory idiopathic uveitis.^{15,26–28} Doses used are described in Table 2.

In a retrospective study of eight eyes from five patients with uveitic cystoid macular edema (CME) refractory to traditional immunosuppressive therapy or anti-TNF- α treatment, Adan et al²⁶ showed that tocilizumab was effective in treating CME at month 1, and as late as 6 months after follow-up. Tocilizumab maintained control of macular edema even after tapering other immunosuppressive agents.²⁶ The same group also published a series involving eleven eyes from seven patients with uveitic CME due to birdshot chorioretinopathy, JIA, and idiopathic panuveitis.²⁷ Both mean logMAR visual acuity and central foveal thickness by optical coherence tomography (OCT) improved after treatment with tocilizumab at the 1 year follow-up. Two patients withdrew from the study due to sustained remission at 12 months, but in both patients, CME relapsed within 3 months after tocilizumab withdrawal. No serious adverse events were reported in this small study of uveitis patients.²⁷ In a separate study, Papo et al²⁸ treated eight consecutive severe refractory uveitis patients with 8 mg/kg of tocilizumab, IV, every 4 weeks. They showed that six out of the eight patients

Table 2 Summary of anti-IL-6 or IL-6R biologics

Biologic name	Molecular target	Company	Studied dosing	Potential uses
Tocilizumab ^{13,15,24,26,27}	Membrane and soluble IL-6 receptor	Genentech	4 or 8 mg/kg IV q4wk for 6 doses or 162 mg SC qwk	RA , JIA, Castleman disease, Behçet disease, systemic sclerosis, uveitis
Sarilumab ³¹	Membrane and soluble IL-6 receptor	Regeneron	150–200 mg SC q2wk	RA, uveitis
Sirukumab ³⁰	IL-6	Janssen	100 mg SC q2wk	RA
Olokizumab ³²	IL-6	UCB	60–240 mg SC q2–4wk	RA
Clazakizumab ³³	IL-6	Alder BioPharmaceuticals	80–320 mg IV on day 1, and week 8	RA
Siltuximab ³⁴	IL-6	Janssen	11 mg/kg IV q3wk	Castleman disease, multiple myeloma, prostate cancer

Note: Bold denotes FDA-approved uses.

Abbreviations: IV, intravenous; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; SC, subcutaneous; q4wk, every 4 weeks; q2–4wk, every 2 to 4 weeks; q3wk, every 3 weeks.

responded to tocilizumab with visual acuity improvement in five patients. Side effects included bronchitis (n=1), leukopenia (n=1), and thrombocytopenia (n=1). Two separate Phase I/II clinical trials are ongoing (www.clinicaltrials.gov) to study the efficacy of tocilizumab in noninfectious intermediate, posterior or panuveitis (STOP-Uveitis) and in JIA-associated uveitis.¹³ A Phase III clinical trial for tocilizumab (also at www.clinicaltrials.gov) in the treatment of sight-threatening Graves orbitopathy not responsive to intravenous corticosteroids is also enrolling patients.

Sirukumab (Janssen Biologics, Horsham, PA Glaxo SmithKline, Brentford, UK), a human monoclonal antibody that binds IL-6, is currently undergoing a Phase III clinical trial for RA not responsive to methotrexate or anti-TNF- α treatment, and is being studied as monotherapy in a comparative efficacy trial with adalimumab.²⁹ Smolen et al³⁰ reported the results of a Phase II study in RA patients refractory to methotrexate. In their study, the primary endpoint of ACR50 scores was achieved at week 12 using sirukumab 100 mg every 2 weeks. ACR50 refers to a 50% improvement in RA as determined by guidelines set forth by the American College of Rheumatology. This is determined by the percentage of improvement in tender and swollen joints.

Sarilumab (Regeneron Pharmaceuticals, Tarrytown, NY, USA) is a human anti-IL-6 receptor monoclonal antibody also undergoing several Phase III clinical trials for use as monotherapy and in conjunction with drugs like methotrexate therapy for RA. In a study in which 306 active RA patients refractory to methotrexate treatment were randomized to 1 of 6 treatment arms of varying doses of sarilumab, the proportion of patients achieving the primary endpoint, based on an ACR20 (20% improvement according to guidelines set forth by the American College of Rheumatology) at week 12, was higher in sarilumab 150 mg weekly or every other

week groups compared with the placebo.³¹ A multicenter Phase II trial, the SATURN Study, to evaluate the efficacy of sarilumab in noninfectious intermediate, posterior, and panuveitis is currently enrolling subjects.¹³

Other IL-6 biologics include olokizumab (UCB, Brussels, Belgium), clazakizumab (Alder BioPharmaceuticals, Bothell, WA, USA), and siltuximab (Janssen, Horsham, PA, USA). Olokizumab is a humanized anti-IL-6 monoclonal antibody that was effective in a 12 week Phase IIb study in RA patients who were refractory to TNF inhibitors.³² Clazakizumab is also a humanized anti-IL-6 monoclonal antibody that achieved its primary endpoint in treating RA patients refractory to methotrexate.³³ Siltuximab (CNTO 328) is a human–murine anti-IL-6 monoclonal antibody, which has been studied in clinical trials for a number of diseases including prostate cancer, renal cancer, ovarian cancer, Castleman disease, and multiple myeloma.^{6,34} Table 2 summarizes the biologics targeting IL-6 or the IL-6 receptor.

Adverse side effects and work up

Commonly reported adverse events that have been reported in the clinical trials for anti-IL-6 or IL-6 receptor antibodies appear to be similar, and include gastrointestinal disorders, respiratory tract infections, urinary tract infections, and nervous system disorders.²⁹ No cases of tuberculosis were reported, although most patients will have received testing to rule out tuberculosis prior to receiving these therapies. Common laboratory findings included neutropenia or other hematologic changes, elevated liver function tests, and elevated serum lipids, although establishing a causal role for these changes with these biologics requires further investigation.^{29–31,33}

Disclosure

The author reports no conflicts of interest in this work.

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