Therapeutic Targeting of the Interleukin-6 Receptor

Toshio Tanaka, Masashi Narazaki, and Tadamitsu Kishimoto

Laboratory of Immunoregulation, Graduate School of Frontier Biosciences, and Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Graduate School of Medicine, Osaka University, Osaka, 565-0871 Japan; email: kishimot@fbs.osaka-u.ac.jp

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Abstract

Interleukin (IL)-6 is a typical cytokine featuring redundancy and pleiotropic activity. It contributes to host defense against pathogens, but dysregulation of IL-6 production plays a significant pathological role in various autoimmune and inflammatory diseases. Because IL-6 blockade was expected to constitute a novel strategy for the treatment of such diseases, tocilizumab, a humanized anti-IL-6 receptor antibody (anti-IL-6RAb), was developed. Clinical trials have demonstrated the efficacy of anti-IL-6RAb for patients with rheumatoid arthritis, Castleman's disease, and juvenile idiopathic arthritis, resulting in approval of this innovative biologic for the treatment of these diseases, and it can be expected to become a novel drug for various other autoimmune and inflammatory diseases. In murine models of autoimmune diseases, anti-IL-6RAb induces Treg and inhibits Th17 and/or Th1 differentiation, indicating that anti-IL-6RAb may be able to repair Th17/Treg imbalance in human diseases as well.

INTRODUCTION

IL-6: interleukin-6

AA: amyloid A

Human interleukin-6 (IL-6) is a secreted 21-kDa glycoprotein with a four-helix bundle structure containing 184 amino acids (1). IL-6 has a wide variety of functions because it acts not only on B cells but also on T cells, hepatocytes, hematopoietic progenitor cells, and fibroblasts (**Figure 1**) (2, 3). In liver, IL-6 strongly induces a broad spectrum of acute-phase proteins such as C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin, antichymotrypsin, fibrinogen, and hepcidin, whereas it reduces albumin, fibronectin, transferrin, and cytochrome P450 (CYP) (4, 5). Changes in the levels of these proteins are commonly observed in acute and chronic inflammatory diseases, and prolonged inflammation leads to a pathological state. For example, high levels of hepcidin block iron transporter ferroportin 1 on macrophages, hepatocytes, and gut epithelial cells, leading to hypoferremia and anemia of inflammation (6), whereas a high level of SAA over long periods results in amyloid A (AA) amyloidosis (7). In lymphocytes, IL-6 induces B cell differentiation into immunoglobulin-producing cells. $CD4^+$ T helper cells show distinct effector functions after their differentiation, and a subset of IL-17-producing T helper cells (Th17) plays a crucial role in the induction of autoimmune tissue injury (8). Combined with transforming growth factor β (TGF-β), IL-6 is essential for Th17 differentiation from naive $CD4^+$ T cells, whereas IL-6 inhibits the generation of regulatory T cells (Treg) induced by TGF-β (8, 9). IL-6 also acts on $CD8^+$ T cells to induce cytotoxic T cells (10). In addition to the effects of IL-6 on acquired immunity,

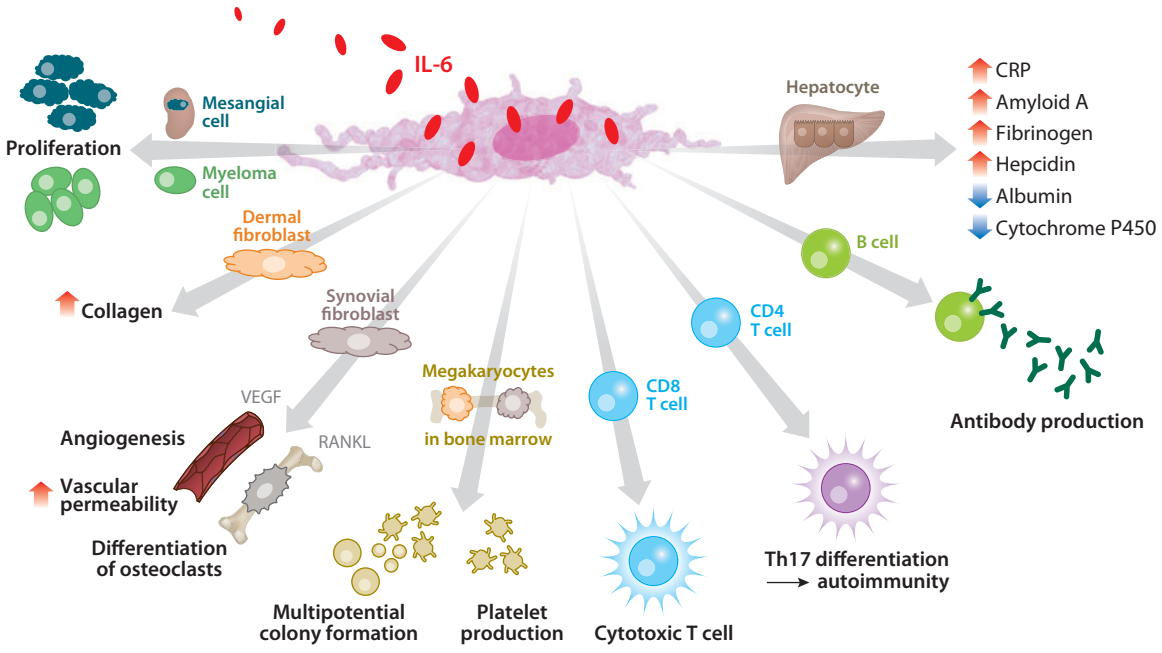

Figure 1

Interleukin-6 (IL-6), a multifunctional cytokine. IL-6 induces cell differentiation and specific gene expression. It induces production of acute-phase proteins such as CRP, amyloid A, fibrinogen, and hepcidin, whereas it reduces synthesis of albumin and cytochrome P450 in hepatocytes. IL-6 promotes immunoglobulin synthesis in activated B cells as well as Th17 and cytotoxic T cell differentiation from naïve T cells. In bone marrow, IL-6 induces maturation of megakaryocytes to platelets and activation of hematopoietic stem cells. IL-6 also acts on synovial fibroblast cells to produce RANKL and VEGF, which promote differentiation of osteoclasts and angiogenesis, respectively. Furthermore, IL-6 stimulates dermal fibroblasts to produce collagen and the growth of cells such as myeloma/plasmacytoma cells and mesangial cells. Abbreviations: CRP, C-reactive protein; RANKL, receptor activator of NF-κB ligand; VEGF, vascular endothelial growth factor.

IL-6 performs an important function as an in vivo SOS signal in the early phase of infections or injuries. In infectious inflammation, IL-6 is produced by monocytes and macrophages after the stimulation of Toll-like receptors (TLRs) with distinct pathogen-associated molecular patterns (PAMPs) of microbes via the myeloid differentiation factor 88 (MyD88)-dependent pathway (11). In noninfectious inflammation, such as burn or traumatic injury, damage-associated molecular patterns (DAMPs) from damaged or dying cells stimulate TLRs to produce IL-6 (12).

RA: rheumatoid arthritis

Anti-IL-6RAb: anti-interleukin-6 receptor antibody

The pathological significance of IL-6 for various diseases has been the subject of numerous reports. The relationship was first demonstrated in a case of cardiac myxoma. The culture fluid obtained from the myxoma tissues of a patient who presented with fever, arthritis with positivity for antinuclear factor, increased CRP level, and hypergammaglobulinemia contained a large quantity of IL-6 (13), which suggested that IL-6 may contribute to chronic inflammation and autoimmunity. Subsequent studies have shown that dysregulation of IL-6 production is implicated in the pathogenesis of Castleman's disease (14), rheumatoid arthritis (RA) (15), and various other autoimmune, inflammatory, and malignant diseases (2, 3, 16–18). In patients with RA, high levels of the IL-6/soluble IL-6 receptor (sIL-6R) complex in synovial fluids induce osteoclast-like cell formation, which is responsible for joint destruction (19). Moreover, IL-6 production in bone marrow stromal cells generates the receptor activator of NF-κB ligand (RANKL), which is an essential factor for the differentiation and activation of osteoclasts and bone resorption (20). Enhanced angiogenesis and vascular permeability of synovial tissue are pathological features of RA resulting from the excess production of vascular endothelial growth factor (VEGF), which is induced by IL-6 in synovial fibroblasts (21). The promotional activities of IL-6 may also contribute to autoimmune skin diseases such as psoriasis owing to the proliferation of keratinocytes or systemic sclerosis owing to the collagen production in dermal fibroblasts (22, 23).

The IL-6 receptor (IL-6R) system consists of two chains: IL-6R, which is the 80-kDa IL-6-binding subunit that has a short cytoplasmic domain (24), and gp130, which is the 130-kDa transmembrane glycoprotein. The latter transduces the IL-6 signal into cells (**Figure 2**) (25). The broad range of expression of gp130 on various cells suggests that IL-6 has pleiotropic effects because naturally occurring sIL-6R is present in human serum. Furthermore, even in cells lacking transmembrane IL-6R, the IL-6/sIL-6R complex can transduce the IL-6 signal on gp130-expressing cells (26). After binding of IL-6 to IL-6R, the resultant IL-6/IL-6R complex associates with gp130, and the activated IL-6 receptor complex is formed as a hexameric structure that includes two molecules each of IL-6, IL-6R, and gp130 (27, 28). The IL-6 signal is transduced into cells via gp130-JAK-STAT3 (signal transducer and activator of transcription 3) and gp130-JAK-SHP-2 (SH2-domain containing protein tyrosine phosphatase-2) pathways (**Figure 2**). IL-6R is a cognate binding receptor for IL-6, whereas gp130 is shared by cytokines of the IL-6 family including leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, IL-11, cardiotrophin 1, cardiotrophin-like cytokine, and IL-27 (29–31). These cytokines often show overlapping functions with those of IL-6 via the common signal transducer gp130.

HUMANIZED ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY (TOCILIZUMAB)

Because of the biological activities of IL-6 and its pathological role in diseases, IL-6 blockade was expected to constitute a novel treatment strategy for inflammatory and autoimmune diseases (17, 18, 32). In response to these expectations, anti-IL-6R antibody (anti-IL-6RAb) (chemical name: tocilizumab) was developed, which is a humanized anti-IL-6R monoclonal antibody of the IgG1 class that was generated by grafting the complementarity-determining regions of a mouse antihuman IL-6R antibody onto human IgG1. Anti-IL-6RAb blocks IL-6-mediated signal

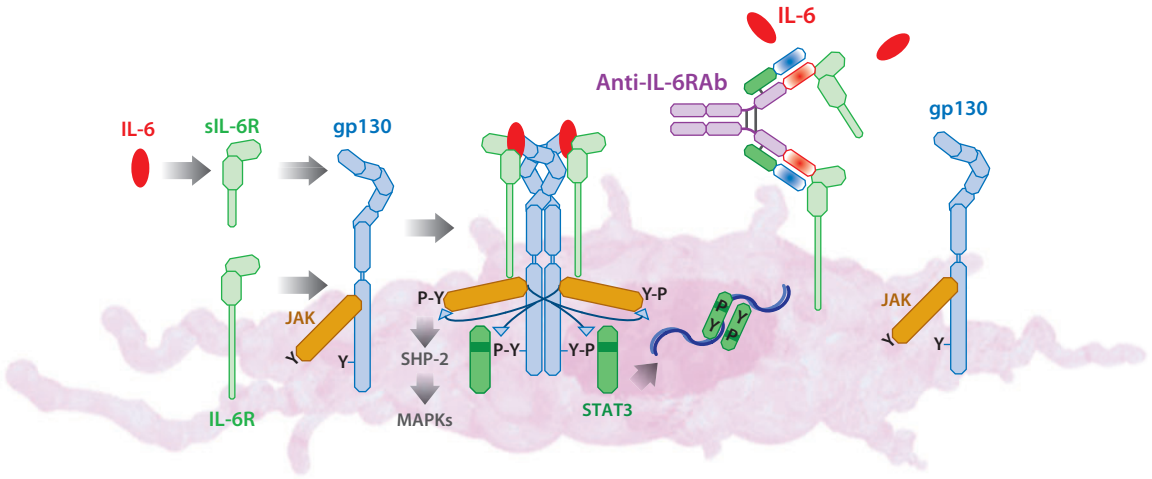

Figure 2

Anti-interleukin-6 receptor antibody (anti-IL-6RAb) blocks IL-6 binding to transmembrane IL-6R and soluble IL-6 receptor (sIL-6R). After binding of IL-6 to interleukin-6 receptor (IL-6R), the resultant IL-6/IL-6R complex associates with gp130 and induces the homodimerization of gp130, which triggers activation of Janus kinase family tyrosine kinases (JAKs) and tyrosine phosphorylation of gp130. The phosphorylated tyrosine motif of gp130 then recruits the signal transducer and activator of transcription 3 (STAT3) via the SH2-domain. Next, activated STAT3 translocates into the nucleus and regulates transcription for various sets of genes. Tyrosine-phosphorylated gp130 also recruits the SH2-domain containing protein tyrosine phosphatase-2 (SHP-2) and induces the association of SHP-2 with adaptor molecule growth factor receptor-bound protein 2 (Grb2), followed by activation of the son of Sevenless (SOS)/Ras–Raf–mitogen-activated protein kinase kinase (MEK)–MAP kinase (MAPK) pathway. Tocilizumab, a humanized anti-IL-6RAb, binds to transmembrane IL-6R and sIL-6R and competitively blocks binding of IL-6 to IL-6R or sIL-6R, leading to the inhibition of IL-6R-mediated signaling.

transduction by inhibiting IL-6 binding to membrane-bound IL-6R and sIL-6R (**Figure 2**). For RA, the recommended anti-IL-6RAb posology in Japan and the European Union is 8 mg kg^{-1} once every 4 weeks. In clinical terms, if free anti-IL-6RAb concentration is maintained at more than 1 μg ml^{-1}, CRP remains negative (33). The concentration of CRP is therefore a hallmark for determining whether IL-6 activity is completely blocked in vivo, although physicians should address the fact that CRP does not function as an acute inflammatory marker during anti-IL-6RAb treatment. Anti-IL-6RAb exposure for RA patients is not affected by concomitantly administered medications such as methotrexate, corticosteroids, and nonsteroidal anti-inflammatory drugs (34), but it may reverse IL-6-induced suppression of CYP activity and thus lead to reduced exposure to certain CYP3A4 substrates (35).

ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY FOR AUTOIMMUNE DISEASES

Rheumatoid Arthritis

RA is a chronic, progressive inflammatory disease of the joints and surrounding tissues characterized by intense pain, irreversible joint destruction, and systemic complications (36). The biological activities of IL-6 as described above and its elevation in serum as well as synovial fluids in patients with RA indicate that IL-6 is one of the key cytokines involved in the development of RA.

Seven Phase III clinical trials of anti-IL-6RAb demonstrated its efficacy either as monotherapy or in combination with disease-modifying antirheumatic drugs for adult patients with moderate to severe RA (37–43). A Cochrane database systematic review concluded that of patients taking

concomitant methotrexate, compared with placebo, anti-IL-6RAb-treated patients were four times more likely to achieve American College of Rheumatology (ACR) 50% improvement (38.8% versus 9.6%) and 11 times more likely to achieve Disease Activity Score remission (30.5% versus 2.7%) (44). Moreover, the SAMURAI (37) and LITHE studies (43) proved that radiological damage of joints was significantly inhibited by the treatment. As a result, anti-IL-6RAb has now been approved for the treatment of RA in more than 90 countries worldwide. The outstanding results obtained with biologics such as anti-IL-6RAb in the treatment of RA led to a change in the treatment objective from protection against joint destruction to prolongation of life expectancy with normal activities of daily living.

SLE: systemic lupus erythematosus

The safety and tolerability profiles of anti-IL-6RAb monotherapy for Japanese RA patients obtained from six initial trials and five long-term extensions have been reported (45). For these studies, 601 patients with moderate to severe RA and with a total exposure of 2,188 patient-years were enrolled. The medial treatment duration was 3.8 years. The incidence of adverse events (AEs), including abnormal laboratory test results, was calculated as 465.1 per 100 patient-years, with infections being the most common serious AEs (6.22 per 100 patient-years). Abnormalities in the laboratory test results, such as increases in lipid and liver function parameters, were common, but most were mild. Of the patients treated for more than 5 years, 59.7% met the Disease Activity Score 28 remission criteria at 5 years, which demonstrates the excellent tolerability and high efficacy of anti-IL-6RAb. A systemic literature review to assess the risk of AEs for RA patients treated with anti-IL-6RAb reported that pooled odds ratios indicated statistical significance for an increased risk of AEs for patients treated with 8 mg kg^{-1} of the antibody plus methotrexate compared with controls (odds ratio = 1.53; 95% confidence interval = 1.26–1.86), as well as a heightened risk of infection (odds ratio = 1.30; 95% confidence interval = 1.07–1.58) (46). However, no increases in the incidence of malignancy or hepatitis were detected. Anti-TNF (anti–tumor necrosis factor) inhibitors significantly increased the frequency of reactivation of tuberculosis (47), whereas anti-IL-6RAb did not produce an increase. In fact, Okada et al. (48) examined the effects of IL-6 and TNFα blockade on the development of tuberculosis infection in mice and observed that there was less tuberculosis infection for anti-IL-6RAb than for anti-TNFα antibody. In addition, we showed that interferon (IFN)-γ synthesis by means of a QuantiFERON®-TB test was suppressed by the addition of anti-TNF inhibitors but not by the addition of anti-IL-6RAb (49).

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown etiology that affects mainly young women (50). The elevation of serum as well as local IL-6 levels of SLE patients indicates that IL-6 plays a pathological role in SLE (51–53). Moreover, mice with epidermal loss of JunB were recently reported to develop SLE phenotype linked to increased epidermal IL-6 secretion, and facial skin biopsies of human SLE patients revealed low JunB protein expression and high IL-6 and activated STAT3 levels within lupus lesions (54). In murine SLE models, IL-6 blockade by means of anti-IL-6RAb or anti-IL-6Ab prevents the onset and progression of the disease (55, 56). An open-label Phase I dosage-escalation study was performed with 16 patients that had mild-to-moderate disease activity (57). The patients were assigned to receive different doses of anti-IL-6RAb (2 mg kg^{-1} for 4 patients, 4 mg kg^{-1} for 6 patients, and 8 mg kg^{-1} for 6 patients) given intravenously every 2 weeks for 12 weeks. Disease activity showed significant improvement in 8 of the 15 evaluable patients, whereas arthritis improved in all 7 patients who had arthritis at baseline. Levels of anti-double-stranded DNA antibodies decreased by a median of 47%. There were no significant changes in total lymphocytes or in overall T or B lymphocyte counts, whereas the frequency of $CD38^{high}CD19^{low}IgD^{-}$ plasma cells, which was higher for SLE patients than

for normal controls (mean 5.3% versus 1.2%), was significantly reduced to 3.1% at 6 weeks. This result indicates that anti-IL-6RAb also represents a promising therapeutic biologic for SLE.

SSc: systemic sclerosis

PM: polymyositis

TA: Takayasu arteritis

GCA: giant cell arteritis

CD: Crohn's disease

Systemic Sclerosis

Systemic sclerosis (SSc) is a connective tissue disease characterized by fibrosis of the skin and internal organs as well as pronounced alterations in the microvasculature (58). IL-6 expression is reportedly high in serum of SSc patients, and its elevation correlates with the skin score (59). Furthermore, in vitro studies have demonstrated that IL-6 may contribute to fibrosis by inducing collagen production (23) and α-smooth muscle actin expression by dermal fibroblasts, which leads to their differentiation into myofibroblasts (60). The clinical effect of anti-IL-6RAb was examined in two SSc patients who had been resistant to conventional treatment regimens. Both patients showed softening of the skin with respective reductions of 52% and 23% in the modified Rodnan total skin score (61). Histological examination showed thinning of the collagen fiber bundles in the dermis. These improvements suggest that anti-IL-6RAb appears to be a promising biologic for the treatment of SSc.

Polymyositis

Polymyositis (PM) is an inflammatory myopathy characterized by the clinical features of progressive symmetrical muscle weakness and mononuclear inflammatory cell infiltrates in muscle tissue (62). PM appears to be another suitable target disease for IL-6R blockade for two reasons. First, excessive expression of IL-6 has been found in the sera and infiltrating mononuclear cells in the muscles of PM patients (63, 64). Second, in models of experimental myositis induced by myosin or C protein, IL-6 blockade by either gene knockout (KO) or anti-IL-6RAb administration showed a preventive or therapeutic effect on myositis (65, 66). We administered anti-IL-6RAb to two PM patients who had been refractory to corticosteroids and immunosuppressive drugs. Creatine phosphokinase levels of both patients normalized, and magnetic resonance images showed the disappearance of high-intensity zones in the thigh muscles (67). These findings suggest that anti-IL-6RAb may also be effective as a novel drug for refractory PM.

Takayasu Arteritis and Giant Cell Arteritis

Takayasu arteritis (TA) and giant cell arteritis (GCA), which involve both large and medium-sized arteries, are examples of vasculitis syndrome. The pathogenesis of TA and GCA remains unclear, but IL-6 is clearly involved in their development (68, 69). Anti-IL-6RAb treatment for a 20-year-old woman with refractory active TA improved the clinical manifestations and abnormal laboratory findings (70), and the antibody treatment induced a rapid remission in 5 patients with GCA and 2 patients with TA (71), which strongly suggests that IL-6 inhibition may become a treatment option for both TA and GCA.

Crohn's Disease

Crohn's disease (CD) is a chronic inflammatory bowel disease of unknown etiology, but IL-6 has been demonstrated to play a significant role in its development (72). Elevated levels of IL-6 have been detected in the blood and in the cultures of colonic mucosal specimens from CD patients (73, 74). In a colitis mouse model generated by transfer of $CD45RB^{high}CD4^{+}$ T cells into SCID mice, anti-IL-6RAb prevented the occurrence of signs and symptoms of colitis (75). A pilot randomized trial of anti-IL-6RAb for 36 patients with active CD demonstrated that 80% of the patients given 8 mg kg^{-1} every 2 weeks showed a clinical response compared with only 31% of placebo-injected patients, indicating that anti-IL-6RAb may also serve as a promising drug for CD (76).

Colitis-associated cancer and intestinal perforation are the most serious complications of inflammatory bowel diseases. IL-6 and STAT3 reportedly play an important role in the survival of intestinal epithelial cells and development of colitis-associated cancer (77), so anti-IL-6RAb might be able to suppress colorectal cancer development. In worldwide clinical trials conducted by Roche, 26 cases of gastrointestinal (GI) perforation were found among RA patients treated with anti-IL-6RAb, and most cases appeared to be complications of diverticulitis (78). The rate for lower GI perforation was 1.9 per 1,000 patient-years, which was substantially lower than the 3.9 per 1,000 patient-years for RA patients exposed to corticosteroids. Although no GI perforation was observed in 23 CD patients treated with anti-IL-6RAb, clinical evaluation to assess whether the treatment leads to a decrease or increase in the incidence of GI perforation in CD patients is essential.

MS: multiple sclerosis

NMO: neuromyelitis optica

Relapsing Polychondritis

Relapsing polychondritis is a rare disease characterized by recurrent inflammation and cartilage destruction (79). Autoimmune reactions to antigens present in cartilage such as type II collagen and matrilin and excess generation of proinflammatory cytokines and chemokines are thought to evoke the disease symptoms (80). The involvement of laryngotracheal cartilage causes severe airway destruction and requires vigorous treatments with corticosteroids and immunosuppressive drugs. Two patients with relapsing polychondritis who had been refractory to conventional regimens were treated with anti-IL-6RAb. The treatment ameliorated clinical symptoms related to upper and lower airways, so that the prednisolone dose could be reduced (81). In one patient, airway narrowing of the bronchus was improved by one year of treatment, whereas in the other patient, gallium citrate uptake in the involved cartilages disappeared 21 months after treatment. Because of the rare occurrence of the disease, there is an urgent need for reports on clinical experience with anti-IL-6RAb in the treatment of relapsing polychondritis.

Acquired Hemophilia A

Acquired hemophilia A is a rare bleeding disorder characterized by the presence of autoantibodies that inhibit coagulation factor VIII (FVIII) activity (82). The etiology remains unknown, but failure of Treg activation may play a crucial role in FVIII inhibitor synthesis (83). Anti-IL-6RAb was administered to a patient with acquired hemophilia A who was refractory to corticosteroids and complicated by diabetes mellitus and glaucoma. The treatment increased the activity of FVIII in a rapid and sustained manner, so that the prednisolone dose could be reduced (84).

Multiple Sclerosis and Neuromyelitis Optica

Multiple sclerosis (MS) is a heterogeneous and complex autoimmune disease characterized by inflammation, demyelination, and axon degeneration in the central nervous system (CNS) (85). The disease may result from a primary defect in the immune system that targets components of the myelin sheath, resulting in secondary effects on neurons. Recent investigations have revealed that autoreactive Th17 and B cells may function as amplifiers and effectors in MS (86). IL-6 or IL-6 transcripts were elevated in the CNS of MS patients and in a murine experimental autoimmune encephalitis (EAE) model of MS (87–89), implicating IL-6 in the development of MS. Moreover, IL-6 blockade by anti-IL-6RAb impeded the development of EAE through the inhibition of antigen-specific Th17 and Th1 (90).

Neuromyelitis optica (NMO) is a chronic inflammatory CNS disorder that predominantly affects the spinal cord and optic nerves (91). Several studies have reported a marked increase of IL-6 in cerebrospinal fluid of patients with NMO (92, 93). Moreover, Chihara et al. (94) recently reported that the population of plasmablasts showing the $CD19^{int}CD27^{high}CD38^{high}CD180^{-}$

JIA: juvenile idiopathic arthritis

phenotype was selectively increased in the peripheral blood of NMO patients and that antiaquaporin 4 (AQP4) antibodies were produced mainly by the plasmablasts. IL-6 enhanced the survival of plasmablasts as well as their AQP4 antibody secretion, whereas anti-IL-6RAb lessened their survival. These findings suggest that IL-6 blockade could be a novel therapeutic strategy for autoimmune neurological diseases such as MS and NMO.

ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY FOR CHRONIC INFLAMMATORY DISEASES

Castleman's Disease

Castleman's disease is a lymphoproliferative disease characterized by benign hyperplastic lymph nodes, follicular hyperplasia, and capillary proliferation accompanied by vascular hyperplasia. Dysregulated IL-6 expression generated by transgenic mice produced a syndrome resembling Castleman's disease (95). IL-6 was highly expressed in hyperplastic lymph nodes of patients with Castleman's disease, and surgical removal of the solitary involved lymph node led to clinical improvement and reduced serum IL-6 concentration (14). This suggests that the generation of IL-6 by hyperplastic lymph nodes is the key element responsible for the various clinical symptoms. In a study by Soulier et al. (96), all HIV-positive and 50% of HIV-negative cases of multicentric Castleman's disease were infected with Kaposi sarcoma (KS)-associated herpes virus (KSHV; also known as human herpesvirus 8). KSHV encodes viral IL-6, which directly binds to and stimulates gp130 in the absence of IL-6R (97). Thus, both viral IL-6 and human IL-6 contribute to the pathogenesis of KSHV-infected Castleman's disease. The first evidence of the beneficial effect of IL-6 blockade was observed in a patient with Castleman's disease treated with a mouse anti-IL-6Ab (98). Subsequently, two open-label clinical trials of anti-IL-6RAb for Castleman's disease showed its marked ameliorative effect in clinical symptoms and laboratory findings (99, 100), leading to approval of anti-IL-6RAb as an orphan drug for Castleman's disease in Japan in 2005.

Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease

Systemic juvenile idiopathic arthritis (JIA) is a subtype of chronic childhood arthritis that leads to joint destruction, functional disability, and growth impairment, accompanied by systemic inflammation (101). IL-6 is markedly elevated in blood and synovial fluid of JIA patients, and their IL-6 level correlates with disease activity (102). A Phase II dose-escalating trial starting with 2–8 mg kg^{-1} of anti-IL-6RAb at 2-week intervals was performed for 11 children with active systemic JIA who were refractory to corticosteroids. Overall improvement in arthritis and systemic features assessed on ACR Pedi 30%, 50%, and 70% improvement scales was seen in 90.9%, 90.9%, and 63.6% of the subjects, respectively (103). A randomized, double-blind, placebo-controlled, withdrawal Phase III trial for 56 patients with systemic JIA showed ACR Pedi 30%, 50%, and 70% responses in 91%, 86%, and 68% of the patients, respectively (104). On the basis of its outstanding efficacy for JIA, anti-IL-6RAb was approved as the first biologic drug for the treatment of systemic JIA in Japan. In a recent global Phase III trial (TENDER), 112 patients with severe systemic JIA who were refractory to conventional treatments, including TNF and IL-1 inhibitors, were randomized to receive placebo or anti-IL-6RAb (8 or 12 mg kg^{-1}, depending on body weight, every 2 weeks). Significantly higher responses for ACR Pedi 50%, 70%, and 90% scales were also noted in the anti-IL-6RAb-treated group at week 12 (85%, 71%, and 37% for the anti-IL-6RAb group versus 11%, 8%, and 5% for the placebo group) (105). Long-term treatment with anti-IL-6RAb has the potential to reserve growth retardation observed in systemic JIA patients because IL-6 inhibits growth hormone signaling (106).

Adult-onset Still's disease (AOSD) is a chronic inflammatory disease characterized by four cardinal symptoms: spiking fever, evanescent maculopapular rash, arthritis, and leukocytosis (107). Pathologically, it resembles systemic JIA and is considered to be an adult-onset type of systemic JIA. Several case and pilot studies have reported that anti-IL-6RAb treatment improved clinical symptoms and signs of AOSD patients who had been refractory to conventional treatments (108–111). The clinical efficacy of anti-IL-6RAb suggests that it may become a first-line biologic for the treatment of systemic JIA and AOSD.

AOSD: adult-onset Still's disease

PMR: polymyalgia rheumatica

RS3PE: remitting seronegative, symmetrical synovitis with pitting edema

Amyloid A Amyloidosis

AA amyloidosis is a serious complication of chronic inflammatory diseases in which amyloid fibril deposition causes progressive deterioration in various organs (7). SAA, an acute-phase protein produced in the liver, is an AA fibril precursor protein, and a sustained high concentration of SAA correlates with a progression of renal amyloid diseases (112). Chronic suppression of SAA levels leads to a regression or stabilization of the amyloid load (113). Because the activation of the SAA gene depends primarily on IL-6 (114, 115), anti-IL-6RAb administration causes a marked reduction of serum concentrations of SAA (40, 99, 100, 116, 117). Three case studies of AA amyloidosis complicated by RA reported on the ameliorative clinical effect of anti-IL-6RAb on GI symptoms due to intestinal amyloidosis (118–120). Surprisingly, AA fibril deposits disappeared in two cases after only three injections of anti-IL-6RAb (118, 120). This suggests that anti-IL-6RAb may be suitable as a first-line drug for patients with chronic inflammatory disease and AA amyloidosis (32).

Polymyalgia Rheumatica and Remitting Seronegative, Symmetrical Synovitis with Pitting Edema

Polymyalgia rheumatica (PMR) is a chronic inflammatory disorder that affects the elderly. PMR is characterized by aching and morning stiffness in the shoulders, neck, and pelvic girdle (68). Although the pathogenesis remains unknown, IL-6 has been identified as the only cytokine present at a consistently high level in patients with the active form of the disease and is recognized as the most sensitive indicator of disease activity (68, 121). Low doses (15–20 mg per day) of corticosteroids are effective, but 65% of patients with PMR experienced at least one steroid-related adverse event in a study by Gabriel et al. (122). Steroid-sparing or alternative drugs thus need to be developed. We reported a significantly beneficial effect of anti-IL-6RAb on a patient with long-standing steroid-refractory PMR complicated by diabetes, osteoporosis, and hypertension (123). After five injections of the antibody, symptoms such as pain and morning stiffness improved and the patient went into remission, so that the prednisolone dose could be reduced. In addition, anti-IL-6RAb treatment produced disease-free status in four patients with PMR complicated by GCA (71). Interestingly, two patients with PMR who were not treated with corticosteroids went into remission.

Remitting seronegative, symmetrical synovitis with pitting edema (RS3PE) is an inflammatory disease characterized by acute onset, symmetrical synovitis, bilateral pitting edema of the hands and feet, and seronegativity for rheumatoid factor (124). The etiology of RS3PE is unknown, but IL-6, produced by the synovial tissues, may play a central role in the development of RS3PE, either directly or through induction of VEGF production, which then leads to synovial hypervascularity and increased vascular permeability (125, 126). Although corticosteroids still constitute the preferred treatment for RS3PE, we reported that anti-IL-6RAb treatment for a case of RS3PE refractory to corticosteroids resulted in improved clinical symptoms and inflammatory laboratory findings such as CRP and matrix metalloproteinase-3 as well as a marked reduction in uptake of

gallium citrate in the bilateral shoulders and hands (127). Serum VEGF levels decreased from 127 pg ml^{-1} to 59 pg ml^{-1}. These case reports suggest that IL-6 blockade may become a novel treatment strategy for PMR and RS3PE.

BD: Behçet's disease

Spondyloarthritides

Spondyloarthritides are a group of disorders characterized by rheumatological manifestations such as axial involvement, peripheral arthritis and enthesopathy, extra-articular features, negativity for rheumatoid factor, and a genetic background with a higher-than-normal positivity for HLA-B27 (128). They include reactive arthritis, ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease–related arthritis.

Reactive arthritis is a disease comprising the clinical triad of arthritis, urethritis, and conjunctivitis (129). The onset of the disease is often preceded by bacterial infections in either the urogenital or GI tract; these infections trigger systemic immunoreactions, and overproduction of proinflammatory cytokines including IL-6 contributes to disease development (130, 131). A 24-year-old woman with sustained active reactive arthritis resistant to conventional treatment regimens for 4 years was treated with anti-IL-6RAb (132). Serum CRP and SAA levels normalized after one injection of anti-IL-6RAb; two injections resulted in the disappearance of joint swelling and pain and complete resolution of symptoms; and after five injections, gallium citrate scintigraphy showed a marked reduction in uptake for the joints.

The clinical benefits of IL-6 blockade with murine anti-IL-6Ab or anti-IL-6RAb for patients with ankylosing spondylitis have also been demonstrated (133–137). It appears that anti-IL-6RAb can substantially improve clinical symptoms of patients with ankylosing spondylitis who were refractory to anti-TNFs, as was also found for the treatment of RA.

Behçet's Disease and Uveitis

Behçet's disease (BD), a systemic inflammatory disease of unknown etiology, is characterized by relapsing episodes of oral aphthous ulcers, genital ulcers, skin lesions, ocular lesions, and other manifestations including neurological, GI, and vascular involvement (138). IL-6 is involved in the pathological development of BD (139, 140). We used anti-IL-6RAb for the treatment of one patient with posterior uveitis who had been suffering from BD for 10 years and had been treated with colchicine, prednisolone, and cyclosporine. Treatment with infliximab, a chimeric anti-TNFα antibody for the recurrent posterior uveitis, brought the attacks of uveitis under satisfactory control. When a severe relapse of posterior uveitis occurred 16 months later, however, anti-IL-6RAb was initiated, and continuous treatment for 1 year reduced the number of ocular attacks and the BD Current Activity Form score (141).

Autoimmune and inflammatory uveitis constitute a group of potentially blinding intraocular inflammatory diseases that arise without a known infectious trigger. They often are associated with immunological responses to unique proteins (142) and often occur in conjunction with systemic diseases. Several studies of animal models indicate that both Th1 and Th17 can play a pathological role in these diseases (143). Blockade of IL-6 signaling was recently reported to suppress autoimmune uveoretinitis (144). The severity of uveoretinitis was similar for wild-type mice, IL-17KO, and IFN-γKO mice, but the inflammatory uveoretinitis was absent in IL-6KO mice. Antigen-specific Th17 and Th1 increased in the IFN-γKO mice and IL-17KO mice, respectively, whereas both populations were reduced in IL-6KO mice. However, Treg depletion in IL-6KO mice caused uveoretinitis, suggesting that the protective effects of IL-6 signaling blockade are mediated by Treg induction and by Th17 and Th1 inhibition. This indicates that anti-IL-6RAb may constitute a therapeutic option for uveitis.

ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY FOR OTHER INFLAMMATORY DISEASES

Case reports have also indicated that anti-IL-6RAb is effective for graft-versus-host disease and TNF-receptor-associated periodic syndrome (TRAPS). A patient with graft-versus-host disease presenting with abdominal pain and diarrhea had been refractory to all known treatments, but after anti-IL-6RAb was administered at 8 mg kg^{-1} every 2 weeks, symptoms improved in conjunction with histological improvement (145). TRAPS is a rare autosomal, predominantly inherited autoinflammatory disease caused by missense mutations of the 55-kDa TNF receptor superfamily 1A and characterized by recurrent episodes of fever, myalgia, arthralgia, migrating erysipelas, and serositis (146). One patient with TRAPS, whose anti-TNF inhibitor or IL-1R antagonist treatment could not be continued, was treated with anti-IL-6RAb. The antibody aborted an evolving acute attack and prevented further attacks of TRAPS (147). These case reports also indicate that anti-IL-6RAb can be effective for other (auto)inflammatory diseases.

CELLULAR AND MOLECULAR MECHANISM OF THE THERAPEUTIC EFFECT OF ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY

Anti-IL-6RAb blocks the binding of IL-6 with 80-kDa transmembrane IL-6R and neutralizes sIL-6R but not IL-6 itself. Anti-IL-6RAb administration initially produces a transient increase in the serum levels of IL-6, but continuous administration subsequently results in a tendency for IL-6 to decrease along with amelioration of the disease activity (33, 148). This suggests that blockade of IL-6 signaling may be able to correct the underlying fundamental immune defects present in various autoimmune and inflammatory diseases. During the past five years, many studies have shown that a balance of new CD4 T cell subsets consisting of Th17 and Treg is important for the pathogenesis of autoimmune diseases. IL-17 produced by Th17 mediates tissue inflammation by promoting synthesis of proinflammatory cytokines including IL-6, whereas it is involved in the elimination of extracellular bacteria through the recruitment and activation of neutrophils and macrophages (8). More importantly, Th17, as opposed to Th1, has been recently recognized as the primary effector cell responsible for the development of autoimmune diseases. In contrast, Treg play a critical role in maintaining immune homeostasis and preventing the development of autoimmune diseases (149); therefore, a balance between Th17 and Treg is crucial for immune homeostasis, whereas an imbalance (Th17$\gg$Treg) causes the onset of various autoimmune and chronic inflammatory diseases. IL-6 in combination with TGF-β promotes the differentiation of naïve T cells into Th17 but inhibits TGF-β-induced Treg differentiation, indicating that IL-6 is an important factor in determining Th17/Treg balance. Dysregulated IL-6 production leads to predominance of Th17 over Treg, whereas anti-IL-6RAb can repair this imbalance (**Figure 3**) (9, 18). Indeed, in several animal disease models, anti-IL-6RAb suppresses antigen-specific Th17 differentiation but induces antigen-specific Treg differentiation (90, 143, 144, 150).

Nuclear receptors, retinoid-related orphan receptors (ROR)γt and RORα, which are induced by IL-6-mediated STAT3 activation, are essential for the induction of Th17 (8). Interestingly, however, IL-27 inhibits Th17 differentiation but does not downregulate the expression of RORγt or RORα (151, 152), suggesting that other nuclear receptor or transcriptional factor may be involved in this differentiation. Stimulation of murine naïve T cells with IL-6 and TGF-β, which are essential for the induction of Th17, induced a marked expression of aryl hydrocarbon receptor (Ahr) (153), which is known as a dioxin receptor. Ahr is present in cytoplasm, and, upon binding with a ligand, it translocates to the nucleus and dimerizes with the Ahr nuclear translocator (Arnt). The resultant Ahr-Arnt complex then binds to specific sequences, designated as xenobiotic

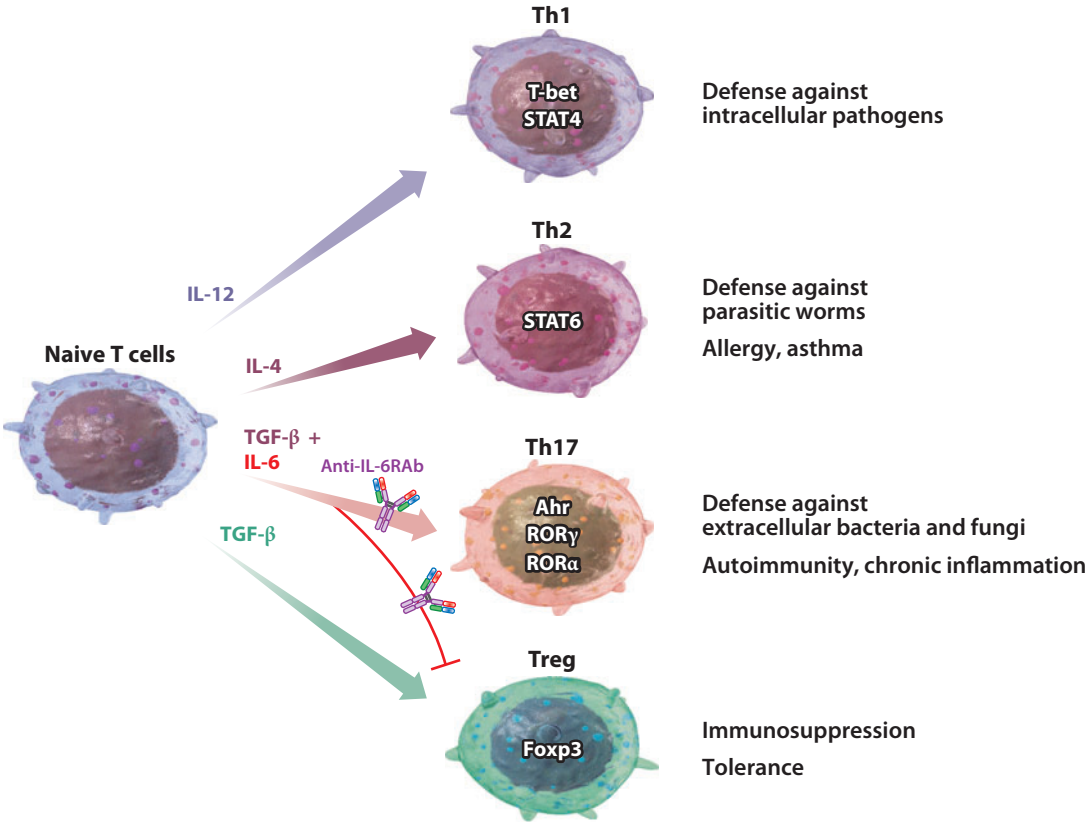

Figure 3

Anti-interleukin-6 receptor antibody (anti-IL-6RAb) may be able to repair Th17/Treg imbalance. When $CD4^+$ naïve T cells are primed, a specific cytokine directs their differentiation into an effector T cell subset. IL-6 in combination with TGF-β preferentially induces Th17 development, whereas IL-6 inhibits TGF-β-induced Treg differentiation, thus leading to Th17/Treg imbalance. This imbalance is pathologically important for the development of autoimmune and chronic inflammatory diseases. Anti-IL-6RAb may be able to repair this imbalance. Abbreviations: Ahr, aryl hydrocarbon receptor; Foxp3, forkhead box P3; ROR, retinoid-related orphan receptor; STAT, signal transducer and activator of transcription; T-bet, Th1-specific T box transcription factor; TGF-β, transforming growth factor β; Th17, IL-17-producing T helper cells; Treg, regulatory T cells.

responsive elements, and exerts a variety of biological effects (154). Moreover, Ahr induced by IL-6 plus TGF-β in T cells interacts with STAT1 and STAT5 but not with STAT3. As reported, STAT3 positively regulates Th17 development by inducing RORγt and RORα, but STAT1 and STAT5 negatively regulate this differentiation. IL-27 or IFN-γ reportedly activates STAT1 (151, 155), and IL-2 activates STAT5, resulting in the suppression of Th17 development by these cytokines (156). These experiments demonstrate that Ahr interacts with both STAT1 and STAT5 and negatively regulates their activities, thus leading to the augmentation of Th17 differentiation by the removal of its negative regulators. As expected, AhrKO mice showed a significant decrease in Th17 development (153) and failed to develop collagen-induced arthritis (157). The induction of EAE is also inhibited in AhrKO mice (158). All these results indicate the importance of the IL-6-Ahr-Th17 axis in the development of autoimmune diseases. Of equal importance is that anti-IL-6RAb may be able to disrupt this axis and repair the Th17/Treg imbalance.

Roll et al. (159) examined 16 RA patients for the in vivo effect of anti-IL-6RAb on the B cell compartment and found that anti-IL-6RAb induced a significant reduction of peripheral preswitch and postswitch memory B cells. As described elsewhere, anti-IL-6RAb treatment leads to a reduction of pathological $CD38^{high}CD19^{low}IgD^{-}$ plasma cells in SLE patients (57), and anti-IL-6RAb can diminish survival of the plasmablast population, which produces mainly AQP4 antibody in NMO (94). These findings suggest that the clinical effect of anti-IL-6RAb is also mediated through its inhibition of pathological autoantibody production.

CONCLUSION AND FUTURE PERSPECTIVES

IL-6 participates in the host defense against environmental pathogens and is involved in a broad spectrum of biological events, such as immune responses, hematopoiesis, and acute-phase reactions, whereas dysregulation of IL-6 production has been implicated in the pathogenesis of various autoimmune and chronic inflammatory diseases. Therapeutic targeting of the IL-6R is therefore considered to be a rational treatment strategy for various diseases (**Table 1**). Although this review has focused on the effects and potential uses of anti-IL-6RAb for autoimmune and inflammatory

Table 1 Therapeutic targeting of the interleukin-6 receptor for various autoimmune and inflammatory diseases

Autoimmune diseases
Rheumatoid arthritis (approved[a] in more than 90 countries worldwide)
Systemic lupus erythematosus
Systemic sclerosis
Polymyositis
Takayasu arteritis and giant cell arteritis
Crohn's disease
Relapsing polychondritis
Acquired hemophilia A
Multiple sclerosis and neuromyelitis optica
Chronic inflammatory diseases
Castleman's disease (approved in Japan)
Systemic and polyarticular juvenile idiopathic arthritis (approved in Japan)
Adult-onset Still's disease
Amyloid A amyloidosis
Polymyalgia rheumatica
RS3PE
Spondyloarthritides
Behçet's disease
Uveitis
Graft-versus-host disease
Autoinflammatory diseases (TRAPS)

[a]Anti-interleukin-6 receptor antibody (anti-IL-6RAb) has been approved as a biological drug for the treatment of rheumatoid arthritis, Castleman's disease, and juvenile idiopathic arthritis and is expected to be applicable to various other autoimmune and inflammatory diseases.

Abbreviations: RS3PE, remitting seronegative, symmetrical synovitis with pitting edema; TRAPS, tumor necrosis factor (TNF)-receptor-associated periodic syndrome.

diseases, it also shows that it is potentially useful for the treatment of malignant diseases including multiple myeloma, renal cancer, prostate cancer, and mesothelioma (17). Clinical trials to evaluate the efficacy and safety of anti-IL-6RAb for these diseases and clarification of the mechanism(s) through which IL-6R blockade exerts its clinical effects constitute important issues for future studies.

SUMMARY POINTS

1. IL-6 plays a significant pathological role in the development of various autoimmune and chronic inflammatory diseases.
2. Humanized anti-IL-6RAb is a first-in-class biologic response modifier with an action different from that of other biologics.
3. Anti-IL-6RAb has proven to be effective for the treatment of RA, juvenile idiopathic arthritis, and Castleman's disease and has been approved for the treatment of these diseases.
4. Anti-IL-6RAb is a promising biologic for various other autoimmune and inflammatory diseases.

FUTURE ISSUES

1. Further clinical trials to evaluate the efficacy and safety of anti-IL-6RAb for various diseases are required.
2. In murine models of autoimmune diseases, anti-IL-6RAb induced Treg and inhibited Th17 and/or Th1 differentiation. However, whether anti-IL-6RAb can repair Th17/Treg imbalance in human diseases remains unknown. The mechanisms through which anti-IL-6RAb is effective for the treatment of diseases need to be elucidated.

DISCLOSURE STATEMENT

Tadamitsu Kishimoto holds a patent for tocilizumab and receives royalties for Actemra®. The other authors declare no conflict of interest.

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