Inhibition of the Interleukin-6 Signaling Pathway: A Strategy to Induce Immune Tolerance

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Abstract Interleukin-6 (IL-6) is a proinflammatory cytokine that is multifunctional, with multifaceted effects. IL-6 signaling plays a vital role in the control of the differentiation and activation of T lymphocytes by inducing different pathways. In particular, IL-6 controls the balance between Th17 cells and regulatory T (Treg) cells. An imbalance between Treg and Th17 cells is thought to play a pathological role in various immune-mediated diseases. Deregulated IL-6 production and signaling are associated with immune tolerance. Therefore, methods of inhibiting IL-6 production, receptors, and signaling pathways are strategies that are currently being widely pursued to develop novel therapies that induce immune tolerance. This survey aims to provide an updated account of why IL-6 inhibitors are becoming a vital class of drugs that are potentially useful for inducing immune tolerance as a treatment for autoimmune diseases and transplant rejection. In addition, we discuss the effect of targeting IL-6 in recent experimental and clinical studies on autoimmune diseases and transplant rejection.

Keywords Inhibition · Interleukin-6 · Signaling pathway · Immune tolerance · Autoimmune diseases · Transplantation rejection · Th17 · Treg

Introduction

Interleukin-6 (IL-6), a B cell-stimulating factor that drives IgG production, is a phosphorylated glycoprotein with a molecular weight of 26 kDa. The human IL-6 gene is mapped to the 7p15-p21 chromosome, which was first cloned and reported by Hirano et al. in 1986 [1].

IL-6 is a classic proinflammatory cytokine that is pivotal in host immune responses, normal cell inflammatory processes, and the modulation of cellular growth. This cytokine is also regarded as a central mediator in chronic inflammatory human diseases and many autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, and Crohn's disease (CD) [2]. Furthermore, IL-6 modulates the resistance of T cells to apoptosis, induces the activation of T helper cells and controls the balance between Th17 cells and regulatory T (Treg) cells [3–5]. Therefore, suppression of IL-6 is seen as a rational strategy for the treatment of a wide range of diseases.

This review will focus on the role of IL-6 in immune tolerance, with a particular emphasis on the results of targeting IL-6 in recent experimental and clinical studies on autoimmune diseases and transplant rejection.

Biological Characteristics of IL-6

IL-6 is produced by various types of lymphoid and other cells, such as T and B lymphocytes, fibroblasts, monocytes, endothelial cells, keratinocytes, mesangial cells, and several tumor cells [6]. IL-6 regulates various physiological processes in multiple tissues, including the production of acute-phase proteins such as C-reactive protein, antigen-specific immune responses, host defense mechanisms, inflammation, and hematopoiesis [7]. Additionally, IL-6 acts as a maturing agent for B lymphocytes and stimulates the synthesis and secretion of immunoglobulins [7]. The cytokine also regulates T lymphocyte activation and differentiation [2]. IL-6 belongs to a family of positive growth regulators, which stimulates the proliferation and differentiation of myeloid cells, along with granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, interleukin-3 (IL-3) and

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interleukin-1 [8]. IL-6 also acts synergistically with IL-3 to support the formation of blast cell colonies and induces macrophage and megakaryocyte differentiation [9]. Moreover, IL-6 upregulates the production of vascular endothelial growth factor and is involved in the recruitment of mesenchymal vascular cells and neoangiogenesis [10].

IL-6 Receptors

There are two types of receptors for IL-6. One is the cell-membrane IL-6 receptor (IL-6R), and the other is the soluble IL-6 receptor (sIL-6R). IL-6R only exists on specific cells, such as macrophages, monocytes, hepatocytes, neutrophils, and T and B lymphocytes, under normal conditions [11]. IL-6R forms a low-affinity complex with glycoprotein 130 (gp130, also called CD130) and starts the intracellular signal (classical signaling) that results from binding to IL-6 [12]. sIL-6R is generated by the shedding of membrane-bound IL-6R via limited proteolysis of the ADAM (a disintegrin and metalloproteinase) gene family members ADAM10 and ADAM17 (90 %) and by mRNA alternative splicing (10 %) [13]. sIL-6R binds to IL-6 and then to the membrane receptor β chain-gp130, leading to signal transduction (transsignaling) [12]. sIL-6R mediates IL-6 signal transduction in a variety of cells, such as endothelial cells, neural cells, and smooth muscle cells, that only have gp130 on their surfaces [14].

IL-6 Signaling Pathways

IL-6 transmits its signals through its unique receptor system. IL-6 interacts with a cell-surface type I receptor complex consisting of the signal-transducing component gp130 and a ligand-binding glycoprotein termed IL-6Ra [12]. There are several signaling pathways for IL-6 [15]:

JAK/STAT3

The activation of Janus kinase (JAK) tyrosine kinases leads to the activation of signal transducer and activator of transcription 3 (STAT3) and tyrosine phosphorylation. After phosphorylation, STAT3 forms a dimer that is then translocated to the nucleus to transmit signals from the cell membrane [16]. The IL-6–JAK–STAT3 pathway regulates the expression of several genes, leading to the induction of proliferation and differentiation. The termination and modulation of this signaling pathway are mediated by the suppressors of cytokine signaling feedback inhibitors and protein inhibitors of activated STAT proteins. These suppressors are induced by activated STAT3 in normal cells under normal physiological conditions.

Ras/MAPK

Ras protein is activated in response to IL-6. Ras activation leads to hyperphosphorylation of mitogen-activated protein kinase (MAPK) and an increase in its serine/threonine kinase activity. MAPK then activates transcription factors that mediate diverse effects, including cell growth stimulation, acute-phase protein synthesis, and immunoglobulin synthesis, depending on the cell type [17].

PI3K/Akt

The enzyme phosphatidylinositol-3 kinase (PI3K) modifies certain phosphatidylinositides to phosphorylate phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3). In turn, PIP3 phosphorylates and activates the serine/threonine kinase PkB/Akt, which is recruited to the plasma membrane [18]. Activated Akt phosphorylates several downstream targets to upregulate cellular survival-related signaling pathways [19].

IL-6 and Th17 Cells

The current consensus is that IL-6, together with transforming growth factor-β (TGF-β), induces Th17 differentiation [20, 21]. The combination of TGF-β and IL-6 induces the expression of orphan nuclear receptors (retinoid-related orphan receptor γt (RORγt) and retinoid-related orphan receptor α (RORα)), which are the key transcription factors that trigger the differentiation of the Th17 lineage [22, 23]. STAT3 regulates IL-6-induced expression of RORγt and RORα and interleukin-17 (IL-17) production [24, 25]. Although IL-6 activates both STAT3 and STAT1, it has been demonstrated that STAT3 activation is maintained while STAT1 activation is suppressed in Th17 cells [26].

IL-6 and Treg Cells

TGF-β is required for Th17 and Treg differentiation and can induce the expression of both Foxp3 and RORγt [27]. However, this induction exclusively leads to Treg differentiation, as Foxp3 can associate with RORγt and inhibit the transcriptional activation of RORγt [27]. In the presence of IL-6, this inhibition is abrogated, and Th17 differentiation is initiated [20, 21]. Thus, IL-6 acts as a potent proinflammatory cytokine by promoting Th17 differentiation and inhibiting Treg differentiation in T cells (Fig. 1). Therefore, control of IL-6 maintains the balance between Th17 and Treg cells and may induce immune tolerance [4].
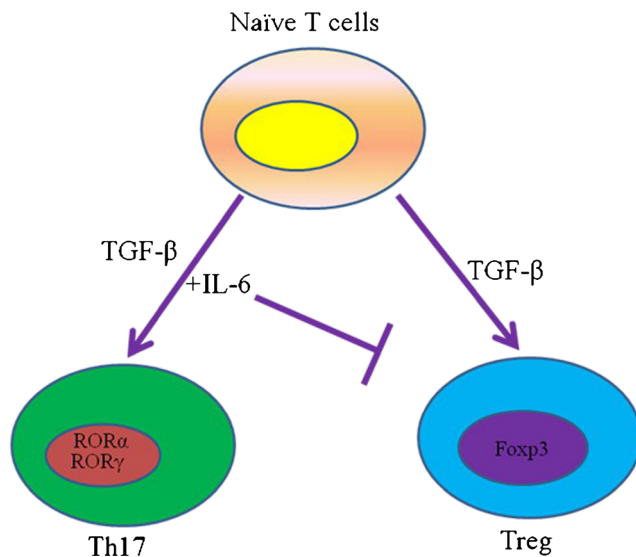
Fig. 1 IL-6 maintains the Th17/Treg balance. IL-6, together with TGF-β, induces Th17 differentiation from naïve T cells. In contrast, IL-6 inhibits the Treg differentiation induced by TGF-β. Abbreviations: RORγ, retinoic acid receptor γ; RORα, retinoic acid receptor α; Foxp3: Forkhead box p3

Th17/Treg and Immune Homeostasis

Th17 cells play a crucial role in triggering inflammation and tissue injury in several autoimmune diseases [28]. Treg cells play a critical role in maintaining immune homeostasis and preventing autoimmune diseases [29, 30]. Therefore, a balance between Th17 and Treg cells is crucial for immune homeostasis [4].

Th17 Cells and Transplant Rejection

Th17 cells are very relevant to transplantation rejection in organ transplantation [31–33]. Rejection was still observed when the signaling pathways of Th1 and Th2 were inhibited in a mouse model of heart transplantation [34]. This rejection was not observed in a mouse model of heart transplantation with a deletion of Th17A [35]. The same results were observed in renal and lung transplantation [36, 37]. Several experimental studies have investigated the contribution of Th17 cells to the development of graft-versus-host disease (GVHD) and have made important observations in various animal models [38–44].

The Th17 differentiation pathway has been shown to play important roles in acute GVHD (aGVHD) [42, 45]. It was shown that the infusion of IL-17-deficient T cells could attenuate chronic GVHD (cGVHD) in the skin and salivary glands in a cGVHD model, which suggests that Th17 cells contribute to cGVHD development [46]. Taken together, these studies suggest that Th17 cells are involved in the development of GVHD and that this effect is mediated both through the direct effects of IL-17 and through indirect effects on the differentiation of other T cell subsets and their local recruitment to GVHD target organs. However, Th17 cells are not necessary for GVHD development, an observation suggesting that Th17 cells interact with other T cell subsets in the pathogenesis of GVHD, including proinflammatory and IFN-γ-releasing Th1 cells and immunosuppressive Treg cells. The importance of Th17 cells relative to the other T cell subsets in the pathogenesis of GVHD seems to differ between various target organs. This organ-dependent variation is likely at least partly caused by local organ-specific variations in the chemokine network and differences in the expression of chemotactic receptors by the various T cell subsets.

The expression of Th17 cells was observed to significantly increase in the phase of acute rejection in patients who had undergone liver transplantation [47]. The expression of Th17 cells significantly increased in patients who had undergone renal transplantation with acute rejection [48]. The expression of Th17 cells was observed in kidney tissues in patients with acute rejection in renal transplantation, although no expression was observed in kidney tissues in patients without rejection [49]. The same result was observed in patients who had undergone lung transplantation [50]. These findings demonstrate an increased Th17 cell population in patients with cGVHD, in addition to an inflammatory process [45, 51, 52]. Th17 cells are associated with cGVHD in patients following hematopoietic stem cell transplantation [53–55]. In one study, the TC and CC genotypes of rs81903036 in the IL-17 gene are associated with an increased risk of aGVHD in patients. Thus, these genetic polymorphisms have an influence on the association with GVHD, suggesting that immunogenetic factors affect Th17 differentiation [56]. A second study described circulating T cells derived from allotransplant recipients with severe treatment-induced cytopenia early after allotransplantation as able to release IL-17, and high levels were observed in patients who later developed aGVHD [57]. This was a small study, so the results should be interpreted with great care; however, the observations support the conclusion of the first study and suggest that IL-17 contributes to the development of aGVHD, at least in acute leukemia patients transplanted with peripheral blood stem cells from family donors and receiving myeloablative conditioning therapy. The number of Th17 cells in a stem cell collection could better predict the risk of aGVHD. A threshold of Th17 cells was not only correlated with cGVHD but was also associated with aGVHD [42, 46, 52, 58–63].

Treg Cells and Immune Tolerance

Treg cells can prevent graft rejection and induce transplantation tolerance [64]. Zheng et al. showed that Treg cells generated ex vivo can act as a vaccine that generates host suppressor cells with the potential to protect MHC-mismatched organ grafts from rejection [65]. In vivo, alloantigen-specific Treg

cells have been shown to prevent rejection initiated by CD4^{+} T cells in both organ and bone marrow transplantation [66, 67]. Treg cells can exert a variety of actions on effector T cells, and especially inhibition of cell proliferation and cytokine and antibody production [68]. For certain donor-recipient combinations, CD8^{+} T cells have a crucial role in graft destruction during both the initiation and the effector phases of the response. Treg cells can suppress allograft rejection mediated by memory CD8^{+} T cells [69]. It has been shown that Treg cells play a pivotal role in transplantation tolerance [70]. Hall et al. demonstrated that upon receipt of a cardiac allograft, rats treated with cyclosporine developed graft-specific unresponsiveness and suppression, which was mediated by Treg cells [71]. Several other studies have also implicated Treg cells in the maintenance of transplantation tolerance [72–76]. Removal of Treg cells from normal mice enhanced graft rejection [77]. When Treg cells were inoculated together with naive T cells and transplanted into syngeneic T cell-deficient mice with allografts, graft survival was significantly prolonged [78]. Various treatments fail to induce allograft tolerance in the absence of the Treg subset, and the suppressive effects mediated by tolerant lymphocytes in adoptive transfer systems are neutralized [72, 75, 79]. Several other studies, such as studies using monoclonal antibodies (mAbs) against CD154, CD4, CD8, or intrathymic antigen inoculation, have demonstrated that transplantation tolerance-inducing methods led to the in vivo generation of Treg cells [66, 80–82]. Many types of immunosuppressive drugs, including nonspecific immunosuppressive drugs after transplantation, are used to avoid acute and chronic rejection in the clinic. These drugs usually consist of calcineurin inhibitors (such as cyclosporine, sirolimus, and tacrolimus), mycophenolate mofetil (MMF), and CD25-specific antibodies. These drugs can induce immune tolerance and the development of Treg cells in cases of organ transplantation [83–93].

Targeting IL-6 and Immune Tolerance

Ratajczak et al. demonstrated that the percentage of Th17 cells was not associated with any evidence of severe tissue damage at cGVHD onset [63]. However, in situ quantification of the Th17/Treg ratio showed that a high Th17/Treg ratio was correlated with severe clinical and pathological GVHD, which argued against a pathogenic role for the Th17 subset [94]. It is thus very important to induce immune tolerance to inhibit the production of Th17 cells and to promote the production of Treg cells. IL-6 has a very important role in regulating the balance between Th17 and Treg cells. The two T cell subsets play prominent roles in immune functions: Th17 cells are key players in the pathogenesis of autoimmune diseases, and Treg cells function to restrain excessive effector T cell responses. IL-6, together with TGF-β, induces the development of Th17

cells from Th0 cells, whereas IL-6 inhibits TGF-β-induced Treg differentiation [28, 29]. Thus, IL-6 acts as a potent proinflammatory cytokine toward T cells through the promotion of Th17 differentiation and the inhibition of Treg differentiation. A low Th17/Treg ratio is required in immune tolerance. Thus, targeting IL-6 is very important in immune tolerance (Fig. 2).

Targeting IL-6 in Autoimmune Diseases

Preclinical and translational findings indicate that IL-6 plays an important role in autoimmune disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis (PM), Takayasu arteritis (TA), giant cell arteritis (GCA), and Crohn's disease (CD), and provides a biologic rationale for targeted therapeutic investigations [95–97]. Past success in treating certain diseases with drugs that antagonize IL-6 signaling has provided further support for a pathological role for IL-6. Targeted biological therapies include monoclonal antibodies (mAbs) directed against IL-6 and IL-6R, which are now widely studied for their efficacy in treating autoimmune diseases in which IL-6 has a central role.

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 both as a monotherapy and in
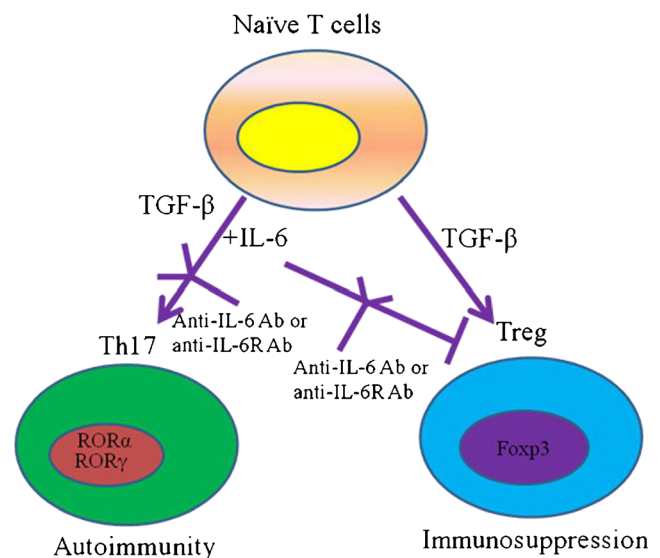
Fig. 2 IL-6 blockade by anti-IL-6Ab or anti-IL-6RAb may modify a Th17/Treg imbalance. IL-6, together with TGF-β, induces Th17 differentiation from naive T cells, whereas IL-6 inhibits Treg differentiation. A Th17/Treg imbalance is believed to lead to the development of various autoimmune diseases and transplant rejection. Continuous treatment with anti-IL-6Ab or anti-IL-6RAb may repair such an imbalance. RORγ and RORα are master transcriptional regulators for Th17 cells, and Foxp3 is a master transcriptional regulator for Treg cells. Abbreviations: RORγ, retinoic acid receptor γ; RORα, retinoic acid receptor α; Foxp3: Forkhead box p3

combination with disease-modifying antirheumatic drugs for adult patients with moderate to severe RA [97–103]. A Cochrane database systematic review concluded that anti-IL-6RAb-treated patients taking concomitant methotrexate compared with placebo were four times more likely to achieve American College of Rheumatology (ACR)-defined 50 % improvement and 11 times more likely to achieve disease activity score remission [104]. Moreover, radiological damage of joints was significantly inhibited by the treatment [97, 103]. As a result, anti-IL-6RAb has now been approved for the treatment of RA in more than 90 countries worldwide. A Japanese study demonstrated the safety and tolerability of anti-IL-6RAb monotherapy in RA patients [105]. A systemic literature review also demonstrated the safety and tolerability of treatment with anti-IL-6RAb at 6 mg kg^{-1} [106].

IL-6 plays a pathological role in SLE [107–109]. Treatment with anti-IL-6RAb also represents a promising therapy for SLE patients and mice. In murine SLE models, IL-6 blockade with anti-IL-6RAb or anti-IL-6Ab prevents the onset and progression of the disease [110, 111]. An open-label phase I dosage-escalation study showed that the disease activity in 8 of 15 evaluable patients with SLE significantly improved with treatment with different doses of anti-IL-6RAb (2 mg kg^{-1} for four patients, 4 mg kg^{-1} for six patients, and 8 mg kg^{-1} for six patients) [112]. The other clinical studies also showed that IL-6 plays a pathological role in SLE and that treatment with anti-IL-6RAb was effective for SLE patients [113–117].

IL-6 expression is reportedly high in the sera of SSc patients, and its elevation correlates with the skin score [118]. Treatment with anti-IL-6RAb appears to be a promising therapy for SSc patients. 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 and thinning of the collagen fiber bundles in the dermis during histological examination [119].

The expression of IL-6 was found in the sera and in infiltrating mononuclear cells in the muscles of PM patients [120, 121]. IL-6 blockade by either gene knockout or anti-IL-6RAb administration showed a preventive or therapeutic effect on myositis in models of experimental myositis induced by myosin or C protein [122, 123]. In the clinic, two PM patients who had been refractory to corticosteroids and immunosuppressive drugs were treated with anti-IL-6RAb. The level of creatine phosphokinase was normal, and high-intensity zones disappeared in the thigh muscles, based on magnetic resonance images [124]. Thus, anti-IL-6RAb may also be effective as a novel drug for refractory PM.

IL-6 is clearly involved in the development of TA and GCA [125, 126]. Clinical manifestations and abnormal laboratory findings were improved after treatment with anti-IL-6RAb for a woman with refractory active TA [127]. Rapid remission was observed in five patients with GCA and two patients with TA when they received treatment with anti-IL-6RAb [128]. IL-6

has also been demonstrated to play a significant role in CD development [129]. In a colitis mouse model, anti-IL-6RAb prevented the occurrence of signs and symptoms of colitis [130]. A pilot randomized trial showed that a high clinical response was achieved for patients with active CD who received treatment with anti-IL-6RAb [131]. Anti-IL-6RAb is also efficacious for the treatment of other autoimmune diseases [132–134].

Targeting IL-6 and Transplantation Tolerance

As we report above, Th17 cells and IL-6 contribute to the mechanisms of rejection after transplantation and IL-6 is a vital factor in the imbalance of Th17 and Treg cells [4, 20–27]. IL-17 participates in the process of acute rejection of organ transplantation [51, 135]. Treg cells can induce immune tolerance after transplantation [64–79]. Thus, the investigation of Th17 and Treg cells in GVHD is especially important [136]. Indeed, in several animal models of disease, anti-IL-6R antibodies have been demonstrated to suppress antigen-specific Th17 differentiation and to induce antigen-specific Treg cells [4, 134, 137–139].

Tawara et al. used a series of complementary knockout and antibody blockade strategies to analyze the impact of IL-6 in multiple clinically relevant murine models of GVHD [140]. The results showed that deficiency in IL-6 in donor T cells led to prolongation of survival. Complete inhibition of IL-6 with anti-mouse IL-6R caused a decrease in GVHD and an even greater reduction in GVHD-induced mortality and preserved a sufficient graft-versus-tumor effect. The reduction in GVHD was independent of the direct effects on T cell effector expansion and donor Treg cells. Huu et al. examined the effects of anti-IL-6R mAb on either the prevention or the treatment of murine sclerodermatous cGVHD (Scl-cGVHD) in a murine model [141]. The researchers found that administration of anti-IL-6RAb attenuated the development of severe Scl-cGVHD and fibrosis. Thus, IL-6 blockade may be an effective approach for preventing Scl-cGVHD and treating cGVHD and scleroderma in humans. Noguchi et al. showed that anti-IL-6R treatment can inhibit the pathogenesis of CD4^{+} T cell-mediated lethal GVHD against minor histocompatibility antigen [142]. Chen et al. reported that inhibition of the IL-6 signaling pathway by antibody-mediated blockade of the IL-6R markedly reduces the pathological damage attributable to GVHD in a murine model [143]. Jagged2-signaling and TLR signals, except the above pathways described, also joined the mechanism of IL-6 for transplantation rejection through up-regulation of IL-6; additionally, blocking IL-6 can induce immune tolerance and increase the graft survival [144, 145].

In the clinic, a patient with GVHD presenting with abdominal pain and diarrhea had been refractory to all known treatments, but after tocilizumab was administered at 8 mg/kg every 2 weeks, the symptoms improved in conjunction with

histological improvement [146]. A 65-year-old woman who had suffered from acquired hemophilia A derived from cGVHD was successfully treated with anti-IL-6RAb [133]. Drobyski et al. used tocilizumab (an anti-IL-6R mAb) to treat eight patients with refractory aGVHD ($n=6$) or cGVHD ($n=2$) once every 3–4 weeks [147]. The majority of patients with aGVHD had grade IV organ involvement of the skin or gastrointestinal tract, whereas both patients with cGVHD had long-standing severe skin sclerosis at the time of treatment. Four patients (67 %) with aGVHD had either partial or complete responses that were apparent within the first 56 days of therapy. One patient with cGVHD had a significant response to therapy, whereas the second had stabilization of disease that allowed for a modest reduction in immunosuppressive medication use. These results indicate that tocilizumab has activity in the treatment of steroid-refractory GVHD. However, Roddy et al. reported nine patients who had steroid-refractory GVHD and received tocilizumab therapy [148]. All patients had GI involvement, and six patients had two organs involved. The median aGVHD grade was 3 (range 3–4). Two patients (22 %) had a complete response, and two had mixed responses, with CR in one organ but no response in another. Only one of nine patients survived. Six patients (67 %) died from aGVHD. These clinical results showed that tocilizumab has a degree of activity in the treatment of steroid-refractory aGVHD but may not be significantly better than other available agents. Therefore, certain clinical trials are being performing for the treatment of GVHD with anti-IL-6RAb in patients who have undergone allogeneic HSCT because tocilizumab is FDA-approved for treating RA but not GVHD [149].

Effect of IL-6 and Targeting IL-6 on Memory B Cell Class Switching and Other T Cell Subsets

IL-6 is a pleiotropic cytokine and has broad biologic activities in various components of the immune system [150, 151]. IL-6 was initially identified as B cell stimulatory factor 2, which is important for the development of antibody-producing plasma cells [152].

IL-6 causes polyclonal B cell activation, plasmacytosis, and B cell neoplasia, which constitutes an important link between adaptive and innate immunity by mediating the B cell responses involved in autoimmunity [153]. IL-6 is central for the induction and/or maintenance of plasma cells that produce immunoglobulin subclasses. In IL-6, knockout mice have shown a marked reduction in B cell immune responses, particularly reductions in the levels of IgG1, IgG2a, and IgG3 on immunization with a T cell-dependent antigen [154, 155]. A recent study showed that antibody production is indirectly promoted by B cell helper capabilities of CD4$^+$ T cells through increased IL-21 production with IL-6 stimulation [156]. The role of B cells in the pathogenesis of RA has also become more widely appreciated in the recent years [157]. B cell differentiation and selection in the inflamed synovium, including the formation of ectopic follicular structures, is a key finding in RA [158]. Treatment of the B cell compartment for patients with RA with anti-IL-6RAb showed that anti-IL-6RAb induced a significant reduction in the frequency of peripheral preswitch and postswitch memory B cells, and the number of IgG$^+$ and IgA$^+$ B cells declined and correlated well with reduced serum immunoglobulin levels [159–161].

The immunologic responses for transplantation rejection are mainly regulated by T cell subsets, especially helper T cells [162]. In particular, CD4$^+$ T cells play a central role in transplantation rejection [37, 163–166]. CD4$^+$ T helper cells can be subdivided into Th1, Th2, Th17, and Treg subsets based on the production of signature cytokines on activation. In the case of the Th1/Th2 dichotomy, the characteristic cytokines are the following: IFN-γ (Th1) versus IL-4, IL-5 (Th2), Th1 increased GVHD, and Th2 decreased GVHD [167–169]. IL-6 inhibited Th1 responses and enhanced Th2 responses [130, 170–173].

Conclusion

IL-6 contributes to the mechanisms of autoimmune diseases and transplantation rejection. The balance between Treg and Th17 cells is mediated by IL-6. Inhibition of IL-6 production, receptors, and signaling pathways are strategies to develop novel therapies for inducing immune tolerance. Currently, more attention should be paid to transplantation rejection, especially in GVHD prevention of haploidentical hematopoietic stem cell transplantation for the treatment of anti-IL-6 Ab or anti-IL-6RAb. Therefore, large, well-designed, double-blinded, randomized, and controlled clinical trials should be performed to verify the role of inhibition of the interleukin-6 signaling pathway in transplantation tolerance.

Conflict of Interest The authors have no conflicts of interest.

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