Low-dose IL-2 in the treatment of immune-related diseases

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Abstract
Since the discovery of interleukin-2 (IL-2) in 1979, increasing attention has been focused on its role in regulating immune function. IL-2 has been found to play an important role in maintaining autoimmune tolerance, and it is essential for the proliferation and differentiation of regulatory T cells (Treg) cells. Other studies have found that the role of IL-2 in vivo is closely related to its concentration. Low-dose IL-2 selectively stimulates the proliferation of Treg cells in vivo, while high-dose IL-2 primarily promotes the proliferation of effector T cells. In view of these findings, an increasing number of studies have focused on the use of low-dose IL-2 in the treatment of immune-related diseases in recent years. The results have been encouraging, with mild adverse reactions. This article mainly focuses on the latest progress made in the IL-2 treatment of immune-related diseases and its regulatory effect on the immune status in different diseases, providing a reference for the rational clinical application of IL-2.

Keywords
interleukin-2, immune tolerance, regulatory T cells, effective T cells

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Background
Since the discovery and naming of interleukin-2 (IL-2) in 1979, increasing attention has been paid to its role in regulating immune function. In the early stage of research, IL-2 was considered to play an important role in promoting T cell proliferation and activation. In the 1980s, the FDA approved IL-2 for the treatment of melanoma and renal cell carcinoma. However, due to its short half-life, approximately 15 min, the clinical treatment dose for these conditions is often as high as 60,000–720,000 IU/kg administered once every 8 h, resulting in many adverse reactions, including fever, joint pain, vascular leakage syndrome, pulmonary edema, and liver and kidney function damage. Moreover, only approximately 5%–10% of patients benefit from treatment with IL-2. Nevertheless, IL-2 has been found to play an important role in maintaining the body’s autoimmune tolerance, and it is also necessary to maintain the proliferation and differentiation of Treg cells. A low dose of IL-2 can selectively stimulate the proliferation of Treg cells in vivo, while effector T cells show no response to low concentrations of IL-2.

IL-2 exerts its biological activity by acting on the IL-2 receptor (IL-2R) located on the cell membrane. IL-2R is a complex composed of CD25 (IL-2Rα chain, 55 kD), CD122 (IL-2Rβ chain, 75 kD), and CD132 (IL-2Rγ chain, 64 kD). In Treg cells, the affinity of trimeric IL-2R (IL-2αβγ) for IL-2 (Kd ≈ 10⁻¹¹) is significantly higher than that in effector T cells (Kd = 10⁻⁸) expressing only dimerized...
IL-2R (IL-2 αβ). After IL-2R specifically binds to IL-2, its configuration changes, inducing signal transduction through three pathways: the JAK/STAT5 pathway, P13K/AKLI/mTOR pathway, and mitogen-activated protein kinase (MAPK) pathway. Finally, IL-2 binding to IL-2R can inhibit cell apoptosis, induce cell proliferation and differentiation, and produce a variety of biological effects. In view of these outcomes, an increasing number of studies have applied low-dose IL-2 to the treatment of immune-related diseases, and many encouraging effects have been achieved with mild adverse reactions. The authoritative literature has reported that the current specific dose range for low-dose IL-2 is 5.4 million IU ≥ single dose ≥ 0.09 million IU and that 1.5 million IU ≥ cumulative dose ≥ 52.5 million IU.

This article mainly focuses on the latest advancements in using IL-2 for the treatment of immune-related diseases and on its regulatory effect on the immune status in the context of various diseases to provide a reference for the rational application of IL-2 in clinical practice.

**Graft versus host disease (GVHD)**

Graft versus host disease (GVHD) is a systemic inflammatory reaction mainly caused by an excessive immune response of T cells and B cells to autologous and allogeneic cells. It is the primary cause of death and complications after allogeneic hematopoietic stem cell transplantation (HSCT). Glucocorticoids are the most important treatments for GVHD, but many patients experience adverse reactions upon their long-term use.

Treg cells play an important role in maintaining immune tolerance, and the number of Treg cells in the peripheral blood of patients with GVHD after transplantation is often significantly decreased. Adoptive Treg cell infusion and other means to enhance the number of Treg cells are new strategies for the treatment of GVHD. Edinger m et al. found that adoptive infusion of donor CD4+ CD25+ Treg cells inhibited GVHD without affecting the host graft antitumor effect. Brunstein CG et al. reported that adoptive transfer of Treg cells cultured in 0.1–30 × 10^5/kg umbilical cord blood efficiently attenuated GVHD in 23 patients who received umbilical cord blood transplantation. The incidence of grade II-IV acute GVHD in these patients was significantly lower than in patients without Treg cell infusion (43% vs 61%). Anke Theil et al. developed a protocol for the efficient isolation and in vitro expansion of donor-derived Treg cells. The final products were used to treat five patients; two of the five patients showed a clinical response with improvement of cGVHD symptoms. The other three patients showed stable cGVHD symptoms for as many as 21 months.

In 2013, a functional defect in IL-2 was found in GVHD patients, which led to the downregulation of Treg cells. As a new therapeutic method, low-dose IL-2 has been used in the treatment of GVHD, which has shown potential therapeutic value. Koreth et al. reported low-dose IL-2 in the treatment of GVHD for the first time. They selected 29 patients with chronic GVHD in the active phase who were refractory to glucocorticoid treatment received increased IL-2 dose escalation trial treatment (0.3, 1, 3×10^6 IU/m2 per day for 8 weeks, and evaluated 4 weeks after discontinuation). The results showed that the safety dose of IL-2 was 1×10^6 IU/m2-d, with no progression or recurrence in any of the patients. The clinical symptoms of 12 patients (52.2%) were improved, and the glucocorticoid dose was reduced to 60% of the pretreatment level. In addition, the number of peripheral CD4+ Treg cells in all patients increased significantly and showed an inhibitory function, while the traditional effector T cells were not affected. In a follow-up Phase 2 study, 35 patients with glucocorticoid-resistant chronic GVHD received IL-2 at 1×10^6 IU/m2 per day. Twenty patients (61%) achieved clinical response, and the shorter the interval was from the beginning of treatment after transplantation or cGVHD, the higher the efficiency of the treatment. An immunological analysis showed that Treg and natural killer (NK) cell numbers increased by 5- and 4-fold, respectively, after treatment, but traditional CD4 effector T cells and CD8 T cell numbers did not change significantly. At a follow-up 2 years after initial IL-2 treatment, two patients had primary recurrence, and one patient had a secondary tumor. The incidence rate was lower than previously reported in the literature. IL-2 is thought to increase numbers of NK cells and thus putatively enhances the antitumor effect in patients. Patients who continued to receive IL-2 were monitored for as many as 2 years, at which time, the clinical symptoms of these patients had continued to improve, and their Treg cells remained at a high level.

To test whether IL-2 dose escalation at the time of anticipation decreases in Treg cell numbers in plasma can circumvent tachyphylaxis and enhance CD4+ Treg cell expansion; Jennifer S Whangbo et al. conducted a phase 1 trial with 10 adult and 11 pediatric patients with steroid-refractory cGVHD. The results showed that low-dose IL-2 was safe and effective in children with advanced cGVHD. However, escalation over the previously defined maximum tolerated dose (1×10^6 IU/m2 per day in children and 2×10^6 IU/m2 per day in adults) did not improve CD4+ Treg cell expansion, nor did it improve the clinical response in adults.

IL-2 can also be combined with other therapies in the treatment of GVHD. Roger Belizaire et al. reported the use of low-dose IL-2 combined with extracorporeal photolysis (ECP) in the treatment of 25 glucocorticoid-resistant chronic GVHD patients. The results showed that the total response rate was 29% in the patients who received ECP after 8 weeks of treatment, but it was increased to 62% in
patients after 8 weeks of continuous treatment with IL-2 (1 \times 10^6 IU/d), and the glucocorticoid dose administered to these patients decreased by an average of 10%. The immunological analysis showed that the number of Treg cells, Treg/Tcon cells, and NK cells in patients receiving the combined treatment was significantly higher than they were before the combined treatment was administered and was significantly higher than they were in the patients for whom the combination therapy was ineffective.

Asano T et al.\textsuperscript{15} examined the changes in inhibitory coreceptors on Treg cells during IL-2 treatment of mouse models and in chronic GVHD patients. Mouse studies have shown that low-dose IL-2 selectively increased the number of Treg cells and increased the expression of programmed death-1 (PD-1), especially in CD44\textsuperscript{+} CD62L\textsuperscript{+} central memory Treg cells, while the expression of other inhibitors (including CTLA-4, LAG-3, and Tim-3) had no significant effect. PD-1-deficient Treg cells showed STAT5 phosphorylation and proliferation soon after IL-2 activation, but then, the Treg cells underwent rapid apoptosis with increased fas and decreased bcl-2 expression levels. Despite continued use of IL-2, the positive effect of IL-2 on the Treg cells was completely eliminated, and the Treg cell levels returned to baseline levels. In clinical trials, patients with chronic GVHD who were treated with low-dose IL-2 also showed increased expression of PD-1 in memory Treg cells. In addition, the improvement of clinical symptoms in patients with GVHD was related to the increase in PD-1 levels on the surface of their Treg cells, which indicated that the PD-1 pathway plays an important role in maintaining Treg cell-mediated immune tolerance.

**Systemic lupus erythematosus (SLE)**

Systemic lupus erythematosus (SLE) is an autoimmune disease that can cause multiple organ failure (MOF). Its pathogenesis involves a variety of immune abnormalities, such as antibodies against autoantigens, immune complexes, abnormally activated immune cells, and inflammatory cytokines. It has also been shown that the number and function of Treg cells are downregulated, which is of great significance in the occurrence and development of SLE.\textsuperscript{16} As early as 1983, it was reported that the level of IL-2 secreted by peripheral blood mononuclear cells was significantly reduced in SLE patients.\textsuperscript{17} Recent study also revealed that a decrease in IL-2 levels in SLE patients is related to the severity of SLE-related nephropathy and 24-h urinary protein levels.\textsuperscript{18} All these findings suggest that IL-2 may be an effective new treatment for SLE. In animal models, IL-2 deficiency and an imbalance in the Treg/Tcon ratio were found in SLE mice, and IL-2 injection improved the immune status of these mice.\textsuperscript{19} In addition, low-dose IL-2 attenuated the symptoms of hypertension in SLE mice by increasing the level of Treg cells.

In terms of clinical trials, Humrich et al.\textsuperscript{20} was the first to report on IL-2 treatment, describing a 36-year-old patient with severe refractory/recurrent SLE who received low-dose IL-2 treatment in 2015. This patient had previously received drugs including glucocorticoids, azathioprine, mycophenolate mofetil, rituximab, cyclophosphamide, bortezomib, and belimumab, but his condition did not improve. The patient then received four cycles of IL-2 treatment of 1.5 \times 10^6 (cycles 1, 3, and 4) and 3 \times 10^6 IU per day (cycle 2), with a cycle comprising five consecutive days with intervals of 9–16 days. After IL-2 treatment, the patient’s Treg cell level increased significantly, SLEDAI score decreased from 14 to 4 points, anti-ds-DNA antibody level decreased significantly, and glucocorticoid dose was reduced from 30 mg/d to 10 mg/d.

Subsequent studies have verified both the therapeutic effect of low-dose IL-2 on SLE and the changes in patient immune status during treatment. Von Speer Mayer et al.\textsuperscript{21} reported that five patients with refractory SLE received low-dose IL-2 at 1.5 \times 10^6 IU/d for five consecutive days. After treatment, the number and proportion of CD4\textsuperscript{+} CD25\textsuperscript{+} CD127-low Treg cells and the expression of Foxp3 and Bcl-2 on Treg cells in all patients were significantly increased, suggesting that low-dose IL-2 selectively increased the Treg cell levels and improved the immune status of these SLE patients. Jing He et al.\textsuperscript{22} administered low-dose IL-2 (1 million IU/d, once every other day, twice per week, for a total of three cycles, with an interval of 2 weeks) to 38 SLE patients. After treatment, the SLEDAI score in 89.5% of the patients decreased by more than four points. The glucocorticoid dose in 91.9% of the patients decreased by more than 25%, and in 67.6% of the patients, the glucocorticoid dose decreased by more than 50%. Furthermore, the immunological analysis of 23 cases showed that the level of CD4\textsuperscript{+} CD25\textsuperscript{+} CD127-low Treg cells was significantly increased after treatment, while the levels of CXCR5+ PD-1+ CCR7low TFH, CCR6+ CXCR3+ CCR7low Th17 and (TFH+ Th17)/Treg cells were significantly decreased. Chunmiao Zhao et al.\textsuperscript{23} reported that in 50 refractory SLE patients treated with low doses of IL-2 (100 WIU, 3–5 days/month, subcutaneous injection) and rapamycin (0.5 mg, once every other day, orally), the number of Treg cells and the balance of Th17/Treg cells were restored.

In conclusion, low-dose IL-2 has demonstrated potential for use in the treatment of SLE. The appropriate selection criteria for patients according to their immune status need to be discerned in future research, and combinations of IL-2 with other drugs may provide new treatments for refractory SLE patients.

**Type 1 diabetes (T1D)**

Many studies have demonstrated that the abnormal function and quantity of Treg cells affect the incidence and
development of T1D immune intolerance.\textsuperscript{24} Low-dose IL-2 has been proven to be a potential therapeutic agent in T1D animal models. Grinberg bleyer y et al.\textsuperscript{25} reported on the use of low-dose IL-2 treatment in the treatment of nonobese diabetic (NOD) mice. The results indicated that the number of Treg cells in the pancreas of these mice was significantly increased, and the expression of related proteins, including Foxp3, CD25, CTLA-4, ICOS, and GITR, on these cells was also significantly increased. In addition, the ability of pancreas-infiltrating T cells to produce interferon gamma (interferon-\(\gamma\)) was also inhibited in these NOD mice. Tang Q et al.\textsuperscript{26} found that the expression of CD25 and Bel-2 in pancreatic islets of the NOD mice was significantly decreased, and that treatment with low-dose IL-2 increased the number of Treg cells and prevented the progression of the disease.

Islet transplantation is an emerging therapy for T1D and hypoglycemic unawareness. Min Hu et al.\textsuperscript{27} reported that the combination of rapamycin with IL-2 (0.3 \(\times 10^9\) IU/m2 or 1 \(\times 10^6\) IU/m2) for 3 weeks in humanized mice significantly prolonged human islet allograft survival associated with the expansion of CD4\(^+\) CD25\(^+\) FOXP3\(^+\) Treg cells and enhanced transforming growth factor-\(\beta\) production by CD4\(^+\) T cells. CD8\(^+\) T cells showed reduced interferon-\(\gamma\) production and reduced expression of perforin-1.

In clinical research, low-dose IL-2 can selectively increase the level of Treg cells in patients with T1D, but its efficacy, optimal dose, and application mode need to be further explored. Long SA et al.\textsuperscript{28} used IL-2 (4.5 million IU/d, 3 times per week for 1 month) combined with rapamycin for the first time to treat nine patients with T1D. The results showed that although the number of Treg cells was significantly higher than that during pretreatment, the islet \(\beta\)-cell function of these patients continued to weaken. Hartemann et al.\textsuperscript{29} also reported that low-dose IL-2 selectively increased the level of Treg cells in the peripheral blood of patients with T1D. In this study, 24 patients were divided into four groups: a placebo group, a 330,000 IU/d IL-2 group, 1 million IU/d IL-2 group, and 3 million IU/d IL-2 group. IL-2 was injected for 5 days and follow-up was performed 60 days after treatment. The results showed that no patients showed serious adverse reactions to the IL-2 treatment and suffered no abnormal glucose metabolism. Rosenzwaig m et al.\textsuperscript{30} also reported that the number and proportion of CD4\(^+\) Foxp3\(^+\) and CD8\(^+\) Foxp3\(^+\) Treg cells in T1D patients treated with low-dose IL-2 were significantly increased. In addition, the expression levels of CD25, GITR, CTLA-4, and pSTAT5 on the surface of the cells in T1D patients were also significantly increased, and the function of islet \(\beta\)-cell antigen-specific Teff cells was inhibited. In their latest study,\textsuperscript{31} they used different doses of IL-2 (0.125, 0.250 or 0.500 million international units (MIU)/m2, given daily in a 5-day course and then every 2 weeks for 1 year) to treat T1DM. The results showed that all doses were safe and that IL-2 induced a dose-dependent increase in the mean proportion of Treg cells, from 23.9% at the lowest dose to 77.2% at the highest dose. There was improved maintenance of induced C-peptide production in the seven Treg cell high responders at 1 year compared with low responders.

### Hepatitis C virus infection–associated vasculitis

Patients with chronic hepatitis C virus (HCV) infection usually have mixed cryoglobulinemia (MC), which is mainly caused by the abnormal activation of B cells and the secretion of autoantigen-specific antibodies. Boyer et al.\textsuperscript{32} found that the number of CD4\(^+\) CD25\(^+\) Treg cells in the peripheral blood of patients with HCV-MC complicated with vasculitis was significantly reduced. M. Baratan et al.\textsuperscript{33} also found that chronic HCV infection could damage and deplete HCV-specific T cells and reduce the secretion of IL-2. These findings provide a theoretical basis for the clinical application of a low-dose IL-2 to selectively improve Treg cell levels during treatment.

Saadoun et al.\textsuperscript{34} reported on the outcomes of low-dose IL-2 treatment of HCV infection-associated vasculitis (1.5 \(\times 10^6\) IU/d \(\times 5\) days in the first week and continued administration of 3.0 \(\times 10^6\) IU/d in the third, sixth, and ninth weeks of treatment). The number of Treg cells was significantly increased in ten patients. Cryoglobulinemia was significantly reduced in nine of ten patients, and the symptoms of vasculitis in eight patients were significantly attenuated. No increase in virus copy number or aggravation of symptoms was detected in any patient.

### Other immune-related diseases

Low-dose IL-2 also shows potential therapeutic value in some other immune-related diseases, including autoimmune hepatitis,\textsuperscript{35} Wiskott–Aldrich syndrome,\textsuperscript{36} autoimmune encephalitis,\textsuperscript{37} corneal transplantation,\textsuperscript{38} alopecia areata,\textsuperscript{39} hypomypathic dermatomyositis with refractory dermatitis,\textsuperscript{40} psoriatic arthritis,\textsuperscript{41} polymyositis, and dermatomyositis.\textsuperscript{42}

Our group also used low-dose IL-2 in the treatment of primary immune thrombocytopenia.\textsuperscript{43,44} After treatment with low-dose IL-2 at 1 million IU/d \(\times 5\) days per week for 2–4 weeks, the platelet count in three of the four ITP patients was higher than before treatment. The proportion of Treg cells in these three patients was significantly higher than it was before treatment, while the level of Treg cells in the 4th patient who did not benefit from the treatment did not change significantly. No adverse reactions occurred in any of the patients.

Why do some patients not respond to low-dose IL-2? Carsten Krieg et al.\textsuperscript{45} reported that high-dose IL-2 treatment...
may affected immune cell lineage marker-negative CD31(+) pulmonary endothelial cells via binding to functional high-affinity IL-2Rαs, expressed at low to intermediate levels on these cells, thus causing pulmonary edema. Therefore, we speculate that the reason for the failure of IL-2 treatment may be due to the presence of IL-2Rαs on endothelial and other nonimmune cells. To address some of the limitations of low-dose IL-2 in enhancing Treg cell activity, the use of mutant IL-2 proteins (mutemice) can be used to improve the selectivity/binding affinity of IL-2 for IL-2R and to clarify the signaling properties of IL-2 by comparing the activity of muteins to that of the wild-type protein. Xi Chen et al. conducted a systematic assessment of IL-2 and IL-2R binding affinity by changing one amino acid at a time in the area of IL-2 that interacts with its receptor IL-2R. One IL-2 mutant, FSD13, showed a greater ability than wild-type IL-2 to stimulate CD4+ T, CD8+ T, and NK cell proliferation; however, it was three-fold less likely than the wild-type protein to induce CD4+ T cell differentiation into Treg cells. Future studies may seek to modify IL-2 to achieve a better Treg stimulatory effect.

Conclusion and future perspectives

In conclusion, treatment with low-dose IL-2 has been used in many immune-related diseases and has achieved encouraging results as an immunomodulator. Currently, the commonly used treatment regimen of low-dose IL-2 is 1–3 million IU/d for more than 5 days. During treatment, the number of Tregs and Tcon cells is monitored, and the treatment course is determined according to the efficacy and compliance of patients. To further explore the therapeutic value of low-dose IL-2 or other drugs that can improve the number and function of Tregs in the treatment of immune-related diseases, the sample size should be expanded, and the appropriate control group selected in future trials. In addition, although IL-2 was one of the earliest cytokines used in clinical practice, many problems still need to be solved, such as how to prolong the half-life of IL-2 in the human body. For different diseases, questions remain: What is the most appropriate therapeutic concentration, dosage, and administration mode of low-dose IL-2 in vivo? The Treg cell levels in some patients with immune-related diseases who received low-dose IL-2 treatment did not increase, and some clinical symptoms of patients with elevated Treg cells were not attenuated. The reasons for these outcomes remain unclear, confusing, and fascinating.

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