Editorial

Low-dose interleukin-2 as a regulatory immunotherapy for systemic lupus erythematosus

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Comment on: He J, Zhang X, Wei Y, *et al.* Low-dose interleukin-2 treatment selectively modulates CD4(+) T cell subsets in patients with systemic lupus erythematosus. Nat Med 2016;22:991-3.

Received: 06 October 2016; Accepted: 03 November 2016; Published: 23 December 2016.
doi: 10.21037/jxym.2016.12.15
View this article at: http://dx.doi.org/10.21037/jxym.2016.12.15

Accumulating evidence that interleukin-2 (IL-2) is requisite for the maintenance and expansion of regulatory T cells (Treg) has yielded low-dose IL-2 therapy for several autoimmune diseases such as type 1 diabetes and systemic lupus erythematosus (SLE) (1,2). He and colleagues recently reported in *Nat Med* the efficacy of low-dose IL-2 treatment in 38 active SLE patients (3). They described that IL-2 treatment significantly ameliorated the clinical severity associated with expansion of Treg and decrease of follicular helper T (T_{FH}) cells and IL-17-producing helper T (T_H17) cells.

IL-2 was first identified as a critical growth factor of T lymphocytes. High-dose IL-2 therapy in melanoma and renal cell carcinoma has been used for more than 20 years in anticipation of expansion of anti-cancer lymphocytes and natural killer cells that are activated and expressed CD25, a high affinity receptor of IL-2. Because IL-2 also plays a critical role for the expansion and function of Tregs, IL-2 supplementation therapy was tried first in mice with type 1 diabetes and revealed that low-dose IL-2 could prevent diabetes progression with significant expansion of Tregs, but high-dose IL-2 did not (4). Shortly thereafter, low-dose IL-2 therapy emerged for the treatment of several human autoimmune and autoimmune-related diseases, and demonstrated selective expansion of Treg cell population associated with clinical response in patients with chronic graft versus host disease (cGVHD) and with chronic hepatitis C-related vasculitis (5,6). In cGVHD, 0.3 to 3 million IU (MIU) of IL-2 were injected subcutaneously daily and the cumulative dosage of IL-2 was 32 to 320 MIU. Treg increase was 8 times higher than controls and NK cells were 2 times higher (5,7). For HCV-associated vasculitis, 1.5 to 3 MIU for 5 days daily for four cycles and up to 50 MIU was used and the therapy led to substantial clinical improvement in both cryoglobulinemia and vasculitis.

In this study by Li and colleagues, 1 MIU IL-2 was administered alternate-day for 7 times at three cycles to active SLE patients. Cumulative dosage was 21 MIU. During and after the course of IL-2 administration, they estimated clinical responses with SLE response index (SRI)-4 response rate (SRI with a 4-point drop in the SLE activity index (SLEDAI)) and the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE disease activity index (SELENA-SLEDAI). Patients were from 18 to 65 at their age without severe chronic liver, kidney, lung, heart dysfunction, infection or cancer. Patients were treated with immunosuppressive agents including corticosteroids for at least 4 weeks and not with high-dose steroid pulse therapy in the last 2 months. Seventeen patients were treated with steroid and hydroxychloroquine (HCQ), 13 with steroid, HCQ and mycophenolate mofetil (MMF) and 7 with steroid, HCQ and cyclophosphamide. Although 2 among 40 patients withdrew before the completion of therapy for non-medical reasons, no serious adverse events or bacterial infections were observed during the 12-week period of treatment. At the end of treatment,

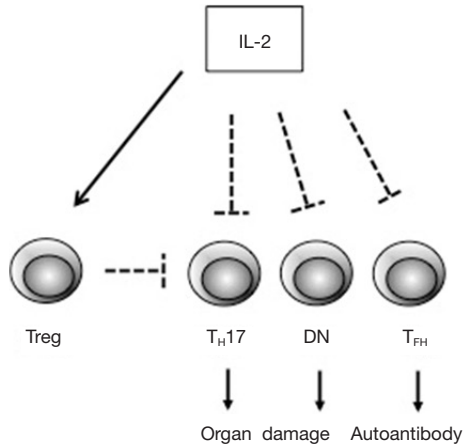

Figure 1 Possible mechanisms of IL-2-mediated immunosuppression. IL-2 expands Treg and could modulate T_H17, DN, T_{FH} cell population. The regulatory effect of IL-2 on T_H17, DN and T_{FH} cells might be mediated either by direct inhibition or through expanded Treg. Arrow: positive regulation, dotted stop lines: direct or indirect negative regulation. Treg, regulatory T cells; T_H17, IL-17-producing T helper cells; DN, TCRαβ$^+$CD3$^-$CD4$^-$ double negative T cells; T_{FH}, T follicular helper cells.

89.5% of patients achieved SRI-4 response rate and SELENA-SLEDAI score was significantly decreased. At week 12, 91.9% of corticosteroid-treated patients could reduce prednisone at a dose by more than 25%.

Low-dose IL-2 therapy in SLE was reported first by Humrich and colleagues in 2015 (8). In that case, subcutaneous injection of 1.5 to 3 MIU IL-2 on 5 consecutive days resulted in disappearance of skin eruption, myositis and reduction of serum anti-ds DNA antibody. SLEDAI score decreased from 14 to 4 and glucocorticoid could be reduced from 30 to 10 mg/day. Percentage of CD4$^+$CD25$^+$Foxp3$^+$CD127^{lo} Treg among CD4$^+$ T cells was transiently upregulated at more than 40%. In the current study by Li and colleagues, they also analyzed peripheral Treg, T_H1, T_H2, T_H17 and T_{FH} cells in blood of 23 patients by flow cytometry. Relative Treg number was significantly increased after 12 weeks of IL-2 treatment and T_H17 and T_{FH} were decreased, whereas T_H1 and T_H2 percentages were not changed. IL-2 is reported to suppress the differentiation of CD4$^+$ T cells into T_H17 cells and T_{FH} cells by a STAT5-dependent mechanism (9,10). Moreover, IL-2 can expand CD4$^+$ PD-1$^+$ CXCR5$^+$Foxp3$^+$ follicular regulatory cells (T_{FR}) and regulate the balance between T_{FH} and T_{FR} leading to the suppression of germinal center formation (11). Therefore, IL-2 could affect the number of T_H17 and T_{FH} cells. Although IL-2 is known to promote the development of T_H1 and T_H2 cells, low-dose administration of IL-2 might not attain the effect on those cells because of lower expression of IL-2 receptors in these cells than Treg (12). Notably, they also assessed the number of T cell receptor (TCR)αβ$^+$CD4$^-$CD8$^-$ double negative (DN) T cells and found that the number was significantly decreased after IL-2 treatment. DN T cells, derived from unknown origin, are known to be expanded in blood from SLE and to favorably produce IL-17 (13). Reduction of DN T cell population by IL-2 also could be involved in the alleviation of disease severity (*Figure 1*).

Low-dose IL-2 treatment for SLE could be a promising, selective therapeutic strategy. However, a number of issues remain to be elucidated. First, could low-dose IL-2 be an alternative to immunosuppressive agents? The conclusion still has a long way to go. In all clinical trials, IL-2 administration was performed as an additional therapy to glucocorticoid and/or other immunosuppressive drugs. Conventional therapy itself has some effect on SLE disease activity and it is unknown whether IL-2 has a specific effect on disease regression or not. Thus far, there are no randomized controlled trials of low-dose IL-2 treatment and further examinations are necessary. It should be noted that the study of He *et al.* (3) compared the results to a control group of patients who were enlisted after the study had added which is unprecedented for clinical trials. Second, how much dosage of IL-2 is required for acquiring substantial effect? IL-2 has a very short half-life in human serum (5–7 minutes) and frequent injection is needed for the induction of effectiveness. The duration of IL-2 treatment could also be a problem. Treg does not seem to increase linearly in response to IL-2 injection after 12 weeks. More studies are needed to define optimal treatment schemes for low-dose IL-2.

Thirdly, the precise mechanisms by which IL-2 alleviates SLE disease severity still remain unclear. Is expanding Treg sufficient for the suppression of autoimmune responses? Lupus T cells have enhanced early CD3/TCR signaling with heightened calcium responses (14). This alteration is in part due to the rewired TCR/CD3 complex. CD3ζ chain is replaced with Fcε receptor 1γ (FcεR1γ, FcRγ) and FcRγ recruits tyrosine kinase Syk instead of Zap70. Nevertheless, IL-2 production of T cells is impaired due to several mechanisms including dephosphorylation of cyclic AMP responsive element binding protein (CREB) through the

excessive phosphatase PP2A activity, aberrant expression of cyclic AMP response element modulator (CREM) and decreased expression of serine/arginine-rich splicing factor 1 (SRSF1) (15). Decreased production of IL-2 in SLE patients likely contributes to various immune defects such as reduced Treg, decreased activation-induced cell death and decreased cytotoxic T cell responses. Aside from the effect of IL-2 on Treg expansion, it is also important to verify the restoration of aberrant and/or impaired T cell functions by IL-2 treatment.

Toward future practical usage of low-dose IL-2 for SLE treatment, randomized controlled study and studies involving large number of patients are necessary.

In Europe, phase II trials are now ongoing with other autoimmune and autoinflammatory diseases. IL-2 might be an old new drug for modulating T cell population to shift them suppressive state. In depth evaluation is required to determine whether the modulation of T cell population directly delivers clinical improvement, and to clarify whether long-term administration is safe and effective.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Yisha Li, MD (Department of Rheumatology, Xiangya Hospital, Central South University, Changsha, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2016.12.15). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jxym.2016.12.15
Cite this article as: Mizui M, Tsokos GC. Low-dose interleukin-2 as a regulatory immunotherapy for systemic lupus erythematosus. J Xiangya Med 2016;1:15.

