Circulating regulatory T cells were absolutely decreased in dermatomyositis/polymyositis patients and restored by low-dose IL-2

We note with interest and express our principle agreement with the views put forward by Professor Rosenzwajg M1 in the recent Editorial ‘Immunological and clinical effects of low-dose interleukin-2 across 11 autoimmune diseases in a single, open clinical trial’ published in *Annals of the Rheumatic Diseases*. The authors conclude that any autoimmune or inflammatory disease denotes a regulatory T cells (Tregs) insufficiency, which is restored by low-dose interleukin (IL)−2 ((1 million IU/day) for 5 days, followed by fortnightly injections for 6 months) selectively and safely activate and expand Tregs in 11 autoimmune diseases. This study is important and deserves a practical value. In our study, the absolute changes of peripheral lymphocyte subpopulations and CD4+ T subsets, especially Tregs, and the safety and efficacy of low-dose IL-2 in dermatomyositis (DM)/polymyositis (PM), which are idiopathic inflammatory myopathies and not shown in the above article, are shared with the readers.

In our study, total 147 patients with PM/DM were enrolled and 128 gender-matched and age-matched healthy adults were participated as controls from February 2016 to October 2018. The absolute numbers of T, B, natural killer (NK), CD4+ T, CD8+ T, Th1, Th2, Th17 and Tregs in peripheral blood of these individuals were detected by flow cytometry combined with standard absolute counting beads. Patients with DM/PM, regardless of new onset (no prior treatment) or treatment with immunosuppressants, had significantly lower absolute numbers of Tregs as well as T, B, NK, CD4+ T, CD8+ T, Th1, Th2 and Th17 than healthy controls (figure 1a,b), which were significantly correlated with disease activity. There were no any significant differences in the numbers of above subsets between new PM/DM and treated PM/DM (figure 1c–f), indicating that those decreases in the subsets are associated directly with the pathogenesis of PM and/or DM rather than high-dose glucocorticoids or immunosuppressive agents. Reduced Tregs should fail to prevent autoimmunity and control inflammation, contributing to the pathogenesis of DM/PM patients. Furthermore, these reductions could be aggravated by conventional therapies, especially immunosuppressive agents, to increase patients’ risk of malignancies and infection.3,5

Total 116 patients in non-IL-2 group were given only conventional treatments while 31 patients in IL-2 group were not only given conventional treatments but also injected subcutaneously.
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human IL-2 (aldesleukin) at 0.50 Million IU/day for a 5-day course. After IL-2 administration, the absolute numbers of Tregs were significantly increased after treatment (figure 2b). Besides, other cells, such as T, B, CD4+ T, CD8+ T, Th1, Th2 and Th17, were also increased mildly to modestly as compared with those before treatment (figure 2a,b). The treatment of short-term and low-dose IL-2 led to a better remission, indicated by a decrease in disease indicators (VAS, ESR, CK, CK-MB, LDH and HBDH) compared with conventional therapy only (figure 2c–h).

Notably, low-dose IL-2 treatment reduced muscle tissue inflammation through specific T reg expansion and activation to balance T eff cells. In addition, other study showed that the treatment can reduce the secretion of chemokines by fibroblasts and thus reduce the migration of peripheral lymphocytes that can

Figure 2  Efficacy of short-term and low-dose IL-2 treatment in regulating levels of peripheral lymphocyte subsets and reducing disease activity. (a) Absolute numbers of lymphocytes, including T, B, CD4+ T and CD8+ T cells in patients were significantly increased after treatment. (b) Absolute numbers of CD4+ T subsets, especially Tregs, were significantly increased in patients after treatment. (c–h) VAS, ESR, CK, CK-MB, LDH and HBDH in all patients were significantly lower than those before treatment. After treatment, VAS in IL-2 group decreased more obviously, while the other indexes of IL-2 group had a trend towards lower values without statistical significance compared with non-IL-2 group. Two-tailed unpaired t-test was used to compare the disease activity measures between IL-2 (red) and control groups (blue). *p<0.05, **p<0.01, ***p<0.001. CK, creatine kinase; CK-MB, creatine kinase MB; ESR, erythrocyte sedimentation rate; HBDH, hydroxybutyric dehydrogenase; IL, interleukin; LDH, lactate dehydrogenase; Tregs, regulatory T cells; VAS, visual analogue scale/score.
further cause muscle damage and creating a loop, which may be one of the reasons for the increase in peripheral lymphocyte subsets and efficacy of IL-2 in DM/PM patients.

In conclusion, our study showed first that there was a decrease in absolute numbers of peripheral T regs in PM/DM patients with or without immunosuppression treatment. Low-dose IL-2, synergising with conventional therapy, can markedly increase the number of Tregs, as well as other lymphocytes to some degree, and maintain the immunologic balance, which may help for DM/PM patients’ symptom remission without over-treatment and evaluated side effect and enhance the ability to resist infection. Our study on DM/PM that was not stated in the study of Rosenzwajg M reconfirmed the involvement of Treg dysfunction in the pathogenesis of autoimmune diseases, which can be restored by low-doses IL-2.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by The Second Hospital of Shanxi Medical University Ethics Committee (2016 KY-007).

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