Response to: 'Circulating regulatory T cells were absolutelydecreased in dermatomyositis/polymyositispatients and restored by low-dose IL-2' by Zhang et al

David Klatzmann

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In this issue, Zhang *et al* report that a short course of low-dose IL-2 improved patients with polymyositis or dermatomyositis. This adds to the list of diseases for which efficacy of low-dose IL-2 has been reported.[1] This is in line with the main activity of low-dose IL-2, the stimulation and expansion of regulatory T cells (Tregs).[1] Tregs are key to maintaining immune homeostasis. They control inflammation and the activation of effector T cells with autoimmune potential.[2] Their depletion immediately unleashes major activation of effector T cells leading to fatal inflammation and the attack of otherwise healthy tissues, leading to multiorgan autoimmunity.[3] This observation indicates that, at homeostasis, there is a balance between Tregs and effector T cells that prevents severe inflammation and autoimmunity. This, in turn, teaches us that any chronic breach of this homeostasis, that is, an autoimmune condition, inherently signals Treg insufficiency.[1] Such Treg insufficiency does not imply a Treg deficiency, but reflects the inability of Tregs to perform properly in their milieu, which comprises the interaction of various molecular and cellular factors including the number and activation state of effector T cells and the cytokine profile. Given these observations, it would appear that the stimulation of Tregs could have therapeutic potential in almost all inflammatory and autoimmune settings. This is well supported by reports of the clinical efficacy of IL-2 in over 30 experimental inflammatory and autoimmune diseases in mice.[1]

In this regard, we recently reported the 'universal' biological effects of low-dose IL-2 across 11 distinct autoimmune diseases[4] assessed in a single 'basket' trial, a design that is common in oncology in which one targeted therapy is evaluated in multiple diseases. We treated patients with diseases that have quite different pathophysiologies, from the most autoimmune to the most inflammatory on the autoimmune-autoinflammatory disease continuum.[5] In this open trial, clinical efficacy was a secondary criterion and showed a significant mean improvement of patients as assessed by a common score. Altogether, with the reports of other groups including Zhang *et al* in this issue, indication of the efficacy of low-dose IL-2 has been reported in over 20 different diseases.

However, it should be stressed that none of these observations have yet been obtained in trials designed to demonstrate efficacy, that is, double-blind, randomised, placebo-controlled trials. Such trials are underway, and some are even completed. Their results will be presented soon at a meeting entirely dedicated to the understanding of the biology and therapeutic potential of IL-2 (https://www.il-2-2019.com). Pending such results, we can already draw important lessons from the published findings.

As the pathophysiology of autoimmune diseases varies greatly, with some being linked to an IL-2 deficiency and others to specific dysregulation of inflammatory pathways, it should be recognised that the potential therapeutic role of IL-2 may vary considerably according to the setting. For example, we foresee that low-dose IL-2 could be the first-line stand-alone drug for the prevention of type 1 diabetes, which is the result of years of chronic Treg insufficiency during which the diabetogenic T cells attack the beta cells.[6] It was recently shown that the onset of type 1 diabetes in at-risk patients can be delayed by acting on the effector response with an anti-CD3 antibody.[7] However, this effect would be difficult to prolong due to frequent antidrug antibodies and some side effects. This would not be the case for IL-2 and we foresee that IL-2 alone could be a first-line treatment in this indication.

In contrast, in many indications, IL-2 could be a second-line or even an adjunct treatment in combination therapies. We foresee that this could be the case for highly inflammatory settings in which the inflammation would have to be cooled down before IL-2 could reach full efficacy, and also possibly in combination treatments that will allow the use of lower doses of the primary drug.

Finally, it should not be forgotten that Tregs not only have anti-inflammatory and anti-autoimmunity activities but also contribute to tissue regeneration.[8] Examples include muscle, for which robust observations show that Tregs contribute to muscle regeneration through amphiregulin production,[9] and IL-2 led to improvement of wound healing.[10] This could explain some of the efficacy observed by Zhang *et al* in myositis, but also opens up the potential use of low-dose IL-2 in settings not often thought about, like myocardial healing after infarction in which Tregs play a major role.[11]

In conclusion, IL-2 is a new class of immunoregulatory drug with an excellent safety profile that should be added to the growing arsenal for single-drug or combination therapy of autoimmune and inflammatory diseases, not to mention transplantation, allergy and tissue regeneration.

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REFERENCES

1 Klatzmann D, Abbas AK. The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases. *Nat Rev Immunol* 2015;15:283–94.
2 Sharabi A, Tsokos MG, Ding Y, *et al*. Regulatory T cells in the treatment of disease. *Nat Rev Drug Discov* 2018;17:823–44.
3 Kim JM, Rasmussen JP, Rudensky AY. Regulatory T cells prevent catastrophic autoimmunity throughout the lifespan of mice. *Nat Immunol* 2007;8:191–7.
4 Rosenzwajg M, Lorenzon R, Cacoub P, *et al*. Immunological and clinical effects of low-dose interleukin-2 across 11 autoimmune diseases in a single, open clinical trial. *Ann Rheum Dis* 2019;78:209–17.
5 McGonagle D, McDermott MF. A proposed classification of the immunological diseases. *PLoS Med* 2006;3:e297.
6 Dwyer CJ, Ward NC, Pugliese A, *et al*. Promoting immune regulation in type 1 diabetes using low-dose interleukin-2. *Curr Diab Rep* 2016;16:46.
7 Herold KC, Bundy BN, Long SA, *et al*. An anti-CD3 antibody, Teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med* 2019;381:603–13.
8 Panduro M, Benoist C, Mathis D. Tissue Tregs. *Annu Rev Immunol* 2016;34:609–33.
9 Burzyn D, Kuswanto W, Kolodin D, *et al*. A special population of regulatory T cells potentiates muscle repair. *Cell* 2013;155:1282–95.
10 Villalta SA, Rosenthal W, Martinez L, *et al*. Regulatory T cells suppress muscle inflammation and injury in muscular dystrophy. *Sci Transl Med* 2014;6:258ra142.
11 Zacchigna S, Martinelli V, Moimas S, *et al*. Paracrine effect of regulatory T cells promotes cardiomyocyte proliferation during pregnancy and after myocardial infarction. *Nat Commun* 2018;9:2432.