Immunotherapy in Type 1 Diabetes: A Shorter but More Winding Road?

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We strive but struggle to translate immune therapies that have been shown to be effective in preclinical models of autoimmune diabetes into use with patients. Only a small proportion of these therapies are actually tested in humans, and of these, efficacy (even short-term) has been achieved in less than a handful (1). A striking example of this struggle is provided by a clinical trial reported in the current issue of Diabetes (2). After setting everything up correctly with convincing data in preclinical models (3,4), an attractive hypothesis (5), and safety studies in animals, the Immune Tolerance Network (ITN) conducted a single-arm trial of combination therapy with interleukin (IL)-2 (4 weeks) together with rapamycin (12 weeks) in patients who had recently developed type 1 diabetes. Treatment (4 weeks) plus successful use of IL-2 receptor and are activated by IL-2. IL-2 therapy did not ignore these IL-2 receptor-bearing cells and in fact led to pronounced transient increases in circulating eosinophils and activated natural killer cells, along with increases in soluble IL-2 receptor concentration. The authors consider these effects on innate immunity to be a likely reason for the exacerbated impairment of β-cell function. This is likely, but this is only guilt by association. If true, one must consider that activation of the innate immune system outweighs the importance of Treg numbers and function. Although the findings of the study do not prove that innate immunity is key in disease pathogenesis, they do suggest that its activation should probably be avoided.

In looking for reasons why there was no clinical benefit, it should not be ignored that IL-2 therapy was given concomitantly with rapamycin therapy. At first sight, rapamycin does not appear to have been particularly harmful. Most of the undesired inflammatory effects occurred during the period of IL-2 therapy and disappeared during rapamycin monotherapy. It is notable, however, that although rapamycin was initially considered anti-inflammatory, it has recently been shown to promote inflammatory pathways (12). Thus, rapamycin may well have contributed to the activation of innate immunity in the first place. Moreover, it has been reported that the addition of rapamycin reversibly hinders efficacy of anti-CD3 therapy in preclinical models of diabetes (13), and rapamycin has similar detrimental effects when added to low-dose IL-2 therapy in NOD mice (E. Piaggio, personal communication). β-Cell function (and normoglycemia) returned quickly after rapamycin withdrawal in these mice. The ITN investigators also suggest that in their trial β-cell function improved after removal of both drugs. However, there were neither β-cell function measures at the end of the 4-week IL-2 therapy nor did the trial include patients who only received IL-2. Thus, we cannot make firm conclusions with respect to rapamycin’s contribution to the impaired β-cell function observed in this report. Perhaps just as critical for the future of IL-2 therapy is whether impairment of β-cell function during treatment really is transient. The total decline in c-peptide observed 12 months after starting treatment was <30%. Reassuringly, this is the same or even less than that observed in others trials. Indeed, optimistically, one could hope that impairment was completely reversible and that with a durable effect on Treg, there will be a net gain for patients.

One practical aspect of the study worth highlighting was the ability to recognize detrimental effects on β-cell...
reserve with a nine patient, no control group study. For this, we can applaud the efforts of TrialNet in conducting and reporting several trials in similar patients and establishing rather tight expectations in C-peptide outcomes after diabetes onset (14). Without contemplating the costs that led to this achievement, it clearly helped the ITN investigators and their Data and Safety Monitoring Board in correctly closing out the study. It is hoped that investigators, industry, and regulatory authorities will recognize these benefits and consider more short-term, well monitored, pilot immune therapy trials in type 1 diabetes.

We (re)learned a great deal about translation from this small clinical study: 1) Pilot trials can be extremely valuable; 2) mechanistic studies can be worth their weight in gold; 3) achieving mechanistic goals does not equal clinical efficacy; 4) “off-target” drug effects should not be ignored; and 5) even with a very convincing rationale, translation is a struggle. Can patients be exposed to IL-2? The compelling evidence for involvement of the IL-2 pathway in type 1 diabetes will rightly lead to more efforts with IL-2 therapy. However, it will be necessary to quickly establish whether functional β-cell loss occurs under IL-2 alone and whether functional loss really is transient or if there is also β-cell loss. If transient, we look forward to finding out how we can obtain positive effects on Tregs without negative effects on effector arms of immunity. The road is slightly shorter, but more winding.

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