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Combination therapies for Type 1 diabetes: why not now?

"...since there is little proof to date that a one-time resetting intervention can eliminate, control or decimate the autoreactive memory pool sufficiently, our options for monotherapies are rather limited at present."



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Type 1 diabetes (T1D), often referred to as juvenile diabetes, is thought to be an autoimmune disease in which insulin-producing β -cells in the islets of Langerhans of the pancreas are being destroyed, resulting in hyperglycemia and the need for lifelong insulin injections. In addition to the impact on quality of life, life-threatening long-term complications can be caused by high blood sugar levels, which predominantly affect the vasculature, resulting in increased risk for heart attacks, strokes, kidney failure, blindness and reduced overall life expectancy. The disease is caused by a complex interplay of genetic and environmental factors and, since the precise cause is not known and the human pancreas is difficult to access, development of an immunotherapy has been slow. However, we have learned important lessons in recent years that should strongly impact upon future therapeutic decisions and, as proposed in this editorial, now lead us to prioritize testing the rationale of combination therapies in clinical trials.

The foremost insight is that T1D, even after successful reversal with cyclosporine or non-myeloablative stem cell therapy (both of which have considerable systemic side effects and, therefore, could not be applied as a generalized intervention) has the unfortunate tendency to recur [1,2]. This is due to the accumulation of β -cell antigen-specific memory T cells, which can expand and react more efficiently, as soon as β -cells are being augmented or reintroduced. This was elegantly demonstrated in recent islet transplantation trials in which the amount of pre-existing autoimmune cells positively correlated with the rapidity of graft loss within 2–4 years [3]. In addition, earlier studies by Sutherland had demonstrated that islets within the pancreas of a nondiabetic twin transplanted into his diabetic sibling were destroyed within months by a recurrent autoimmune attack [4], demonstrating that even new syngeneic β -cells generated from

autologous stem cells would be rapidly annihilated. These facts underline the need for devising a form of immunotherapy that can create long-term tolerance to β -cells while circumventing unacceptable side effects from chronic immunosuppression, most notably secondary cancers [5]. Thus, since there is little proof to date that a one-time resetting intervention can eliminate, control or decimate the autoreactive memory pool sufficiently, our options for monotherapies are rather limited at present [6].

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First, we could try to find an immunomodulatory drug (e.g., one that has already been tested for other autoimmune diseases, transplant or cancer) where repeated treatment is clinically possible. Not many systemically acting compounds fall into this class, since chronic side effects can arise even with comparatively well-tolerated treatments such as Rituxan (anti-CD20) or anti-CD3, both of which have been found to temporarily halt C-peptide decline in recently diagnosed patients (1 and 3–4 years, respectively [7–11]) especially when one has to consider life-long application. Furthermore, generalized and long-term preventive treatment with such drugs, which would also involve some patients who are at risk but in reality would never get T1D, is not ethically feasible. Alternatively, we could develop an antigen-specific treatment that would generate regulatory T cells directed to β -cells, which have very limited (if any) side effects and would allow for chronic treatment. Unfortunately, compared with immune modulators, such vaccines are less

effective [12–14]. However, owing to their excellent side effect profile [13], they might constitute a suitable preventive strategy in the future. Given these considerations, in order to spare us further disappointments with monotherapies and in the interest of time, I would argue that we should now explore possible combination therapies. The advantage and goal of combination therapy would be to reduce side effects (ideally by being able to use lower doses of immune modulators) while enhancing or even synergizing to increase efficacy, which is feasible, at least in animal models [6,15,16].

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In my opinion, an ideal combination would consist of a short-term course of a systemically acting immune modulator to control auto-immune memory-effector cells (i.e., anti-CD3, antithymocyte globulin with GCSF or anti-CD20), a one-time administration of an anti-inflammatory drug immediately following diagnosis (i.e., anti-IL-1R) and long-term therapy with a β -cell protein that can induce regulatory T cells (such as oral or nasal insulin, insulin peptide therapy, GAD-Alum or the proinsulin DNA vaccines), as well as a compound that can have positive effects on β -cells (i.e., exenatide, leptin or other GLP-1 acting drugs). What are the obstacles that would prevent us from beginning such a trial at the present time in individuals with recently diagnosed T1D? Most importantly, and per US FDA guidelines [101], the individual agents have to have proven safety and, ideally, not more than one of them would be an as yet unlicensed drug, which is realizable. Second, for unlicensed drugs, such as anti-CD3, we will need the buy-in from the respective companies,

which could be problematic since there is a generalized reluctance to subject any drug to combination therapy before a single-use label has been obtained. Third, depending on the choice of drugs and vaccines, we will need some animal studies that demonstrate synergy in reversing recent-onset diabetes in the absence of obvious major side effects, since not all compounds are expected to synergize or at least have additive effects [6]. In addition, such studies could be used in conjunction with suitable computer models to optimize the treatment regimen [17].

In conclusion, I would recommend that major diabetes funding bodies, such as the Juvenile Diabetes Research Foundation (JDRF), NIH-National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; TrialNet), NIH-National Institute of Allergy and Infectious Diseases (NIAID; Immune Tolerance Network), Helmsley Foundation and Sanford Initiative, agree on an optimal and feasible combination trial regimen in conjunction with suitable advisors from academia and industry. Indeed, there is already good agreement on prioritization [18], and the amount of additional animal studies and safety studies will probably be limited in scope. If we do not now pursue this goal proactively, I am afraid that we will lose time and opportunities, especially if one considers that some unlicensed drugs might never make it to the market as monotherapies for T1D.

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