Published in final edited form as:

Nat Rev Endocrinol. 2013 July ; 9(7): 384–385. doi:10.1038/nrendo.2013.103.

Immunotherapy for Type 1 Diabetes – targeting the innate immune system

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Abstract

Moran et al report two trials of antagonism of the pro-inflammatory cytokine, IL-1, assessing the monoclonal antibody canakinumab and the IL-1 antagonist, anakinra in new-onset Type 1 Diabetes (T1D). The studies both showed that, although relatively safe, there was no efficacy in terms of halting decline in beta cell function. Is this the end of the line for targeting IL-1 in T1D?

Development of immunotherapy for T1D, an autoimmune disease which can manifest as early as 6 months of age, has been a major research focus, and is particularly important, given the rise in incidence that is greatest in those presenting under 5 years of age. Whereas clinical trials of immunotherapy to date have targeted the adaptive immune system, Moran and colleagues report two separate studies directed against the innate immune system. They focused on antagonizing IL-1 β to reduce inflammation and protect from further loss of beta cells within 3 to 4 months of diagnosis¹. Two forms of anti-IL-1 treatment were used in randomized placebo-controlled trials, in patients shown to have some residual insulin (>0.2 nM C-peptide after mixed meal tolerance stimulation). Antagonism of IL-1 was achieved by the use of anti-IL-1 monoclonal antibody, Canakinumab, as well as by anakinra, the recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra). The only significant adverse events in the treatment groups compared with the placebo, were injection site reactions in the anakinra group. Of importance, neutropenia occurred in both the cankinumab and placebo groups, but in the canakinumab-treated patients, further doses were not associated with subsequent neutropenia.

The multifactorial nature of T1D presents several targets and pathways to consider for immunotherapy. It is generally accepted that T cells, together with an inflammatory environment in the pancreatic islets, play a key role in death of insulin-producing β cells in T1D. Nevertheless, there is a strong environmental component, which suggests that the innate immune system may also play a significant role, especially in the early phases of disease. The long time course, that may span years, leading to development of the islet autoimmune response with loss of insulin production, potentially provides many

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Competing interests statement

The authors declare no competing interests.

opportunities for intervention, if we could predict and safely target the pathogenic players. Once clinical diabetes manifests, the islet autoimmune response with both effector and memory T cells targeting multiple autoantigens is highly developed, making it much more difficult to tackle single components of the disease process.

Why focus on IL-1? IL-1 is a major early inflammatory, widely produced cytokine that has major effects in causing inflammation in response to tissue stress (Figure 1). It is produced by many cell types including macrophages. In addition, islet β cells produce IL-1, in response to hyperglycemia in vitro². Pancreatic islet β cells express IL-1 receptors and signaling through the IL-1 receptor1 (IL-1R1)(Figure 1), together with interferon- γ and TNF- α , not only inhibits insulin secretion but also induces apoptosis³. IL-1 also interfaces with the adaptive immune system, providing a signal for amplification of CD4 T helper cell responses, and for differentiation of IL-17 producing T cells⁴. Furthermore, the inflammatory microenvironment in the pancreatic islets, fuelled by both the immune effectors, as well as by high glucose which is toxic to the beta cell, contributes to damage to beta cells that are highly sensitive to such insults⁵. Thus, both theoretical and experimental evidence of a role for IL-1 in islet β cell inflammation provided a strong scientific rationale⁶ for the studies reported by Moran and colleagues¹.

Anti-IL-1 therapy has been successful in systemic autoimmune conditions that include rheumatoid arthritis, systemic juvenile idiopathic arthritis, and the rare autoinflammatory syndromes such as Familial Mediterranean Fever⁷. This success, together with a preclinical rationale⁶, may have given hope that this treatment would be an alternative route to halting what has been an inevitable decline in beta cell function. Unfortunately, this was not to be. T1D is a very different organ-specific autoimmune disorder to the systemic autoimmune conditions, with a strong T cell contribution. IL-1, produced by macrophages and possibly islet β cells themselves, is likely to be only one of several pathogenic components.

Immunotherapy has generally been tested, of necessity, at the time of onset of diabetes. Did the late stage of disease at which this treatment was tested, contribute to lack of efficacy? There are at least two possible reasons why this might be so. Firstly, the timing of the therapy for single interventions is likely to be very important. Any new therapy that is used at the time of presentation of T1D must take account the late stage of disease, where there are fully activated effector T cells infiltrating the islets, along with B cells and innate immune cells such as macrophages. It is likely that there is an inflammatory islet milieu where β cells, which are highly sensitive to cytokines and oxidative stress, have either been destroyed or those still present have reduced insulin secretion. It could be argued, as IL-1 is likely to play an important role in pathogenesis but the critical effect may be at an earlier stage in disease development, that this therapy may be more effective before clinical manifestation of diabetes. Secondly, given the multi-faceted, fully activated immune response as well as the stressed target beta cells, optimal therapy should address both these factors and a treatment directed at a single component may not be sufficient. Although there are limitations to the use of the animal models of T1D like the non-obese diabetic (NOD) mouse, knocking out IL-1⁸ or IL-1 receptor⁹, as single targeted interventions, had non-statistically significant effects on diabetes development. However, an effective preclinical study using anti-CD3 and anakinra in the NOD mouse has indicated that anti-IL-1 therapy

may be useful in combination with anti-CD3 in NOD mice¹⁰. It should be noted that in this combined therapy study, 10mg anakinra per mouse per day was used, equating to about 400mg/kg (for a mouse weighing ~25g) over a short period of time, whereas in the human study, the approved dose is 250 times less (1.6mg/kg for ~60kg human) over a much longer time course. How this translates would need to be carefully considered.

For the present, as with other unsuccessful treatments used as single agents in clinical trials in T1D to date, anti-IL-1 therapy should not be ruled out. However, we need to consider whether they could be used safely in combination with other agents targeting different aspects of the disease process (Box 1), and whether we could also use treatment at an earlier stage in disease development. These will present both safety challenges as well as hurdles from satisfying drug regulatory authorities, but it will be vitally important to find ways to tackle this.

Box 1

Requirements for optimal immunotherapy for T1D

- Reduce the T cell effector response
- Reduce the T cell memory response
- Increase regulation in the immune system
- Reduce inflammation and restore responses of remaining beta cells
- Regenerate or replace beta cells that will not be subject to further attack

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Figure 1. IL-1 secretion and action on islet β cells

IL-1β is secreted after the IL-1β precursor is cleaved by caspase 1, produced from the NALP3 inflammasome complex of proteins after activation by tissue stress. IL-1β binds to IL-1 receptor 1 (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP), inducing wide-ranging inflammatory effects. The naturally occurring IL-1 antagonist (IL-1Ra) is produced and secreted from cells expressing IL-1, with a circulating concentration of 100–300ng/ml. It binds to IL-1 receptor, but does not induce signaling and antagonizes the effect of IL-1 by competition for binding to the receptor. In islets, IL-1β signals via a number of pathways, ultimately leading to apoptosis. Adapted from ^{6, 7}.