Making progress with immune therapies for type 1 diabetes

Mark Peakman

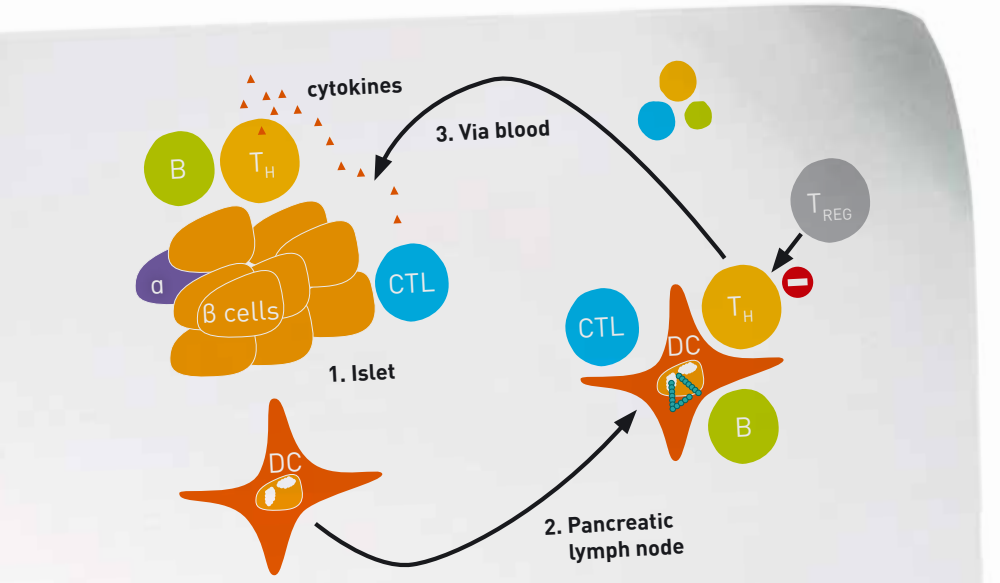
Thirty-five years on from the demonstration that type 1 diabetes has an autoimmune basis, we have learned an enormous amount about the disease. We know its genetic basis (immune genes), its pathological basis (immune cells) and we would expect to be converting this insight into therapeutic advances (immune-based). Certainly, the field of immunotherapy for type 1 diabetes is very active. Here, Mark Peakman reviews the progress being made and scans the horizon for the most likely future breakthroughs.

In the mid-1970s, autoantibodies that bind to targets in cells in the islets of Langerhans were described in the scientific literature. They have since become established as a major biomarker for type 1 diabetes, both at diagnosis and in the preclinical prodrome. We have since learned that the disease results from autoimmune destruction of the insulin-secreting beta cells in the islets, a process involving the T and B lymphocytes and dendritic cells of the immune system (Figure).

Focusing on the beta cells

The disease arises on a distinctive genetic background, in which variants of genes that regulate immune responses are the predominant feature. This understanding, allied with a range of therapeutics (many arising from the field of transplantation), a better understanding of how immunological tolerance is maintained and lost, and several animal models in which new therapies can be tested, has led to a period of intense activity as these advances are translated. Clinical trial consortia, such as Type 1 Diabetes TrialNet and the Immune Tolerance Network, linking centres with expertise in the field to do collaborative research, have been pivotal in promoting the acceptance of study designs that focus on, and are adequately powered to detect, the preservation of beta-cell function (measured as the C-peptide response to a challenge) in new-onset type 1 diabetes, typically measured at six, 12 and 24 months after the introduction of the novel therapy.

Stimulated C peptide has proved an acceptable surrogate for any beneficial effects of therapy in preserving remaining beta cells, which would be expected to have an impact on glycaemic control if sufficient endogenous insulin production remains. A further emerging principle



The insulin-secreting beta cells of the pancreatic islet express proteins (shown in white) that are picked up by dendritic cells (shown in pink) and activate T and B and cytotoxic lymphocytes (green, yellow and blue) to destroy the beta cells, releasing cytokines as they do. Regulatory T cells shown in black can damp down the process.

is that trials are more likely to be able to show benefit if studies are started soon after diagnosis; 100 days from initial presentation to the first administration of the study drug is now the norm.

What kind of therapeutic strategies are emerging?

There are currently two main competing solutions being developed which target components of the immune system. The first is immune modulation via such strategies as biologics that target T lymphocytes, B lymphocytes, co-stimulatory molecules and cytokine pathways, among others (see Figure). This is 'non-specific immunotherapy' is designed to act systemically, making no attempt to target only the minority of T lymphocytes that cause beta-cell damage. The lead compounds here have been two monoclonal antibodies directed against the CD3 protein on the surface of T cells. Although it is not exactly clear how anti-CD3 therapy works, two Phase II studies have indicated beneficial effects on C-peptide decline.

Follow-up studies have even shown the potential for a prolonged effect, with preservation of C peptide for several years in some people. Unfortunately, the data emerging from subsequent Phase III studies ending in 2011 were mixed, although this may be attributable to the study design. Otelixizumab (GlaxoSmithKline/Tolerx, Inc) was reported to have failed Phase III trials in March 2011. The anti-CD3 antibody Teplizumab, developed by Macrogenics and Eli Lilly, also did not meet endpoints in a Phase III trial in type 1 diabetes but published data indicates that C peptide was nonetheless preserved.

It is to be hoped that these drugs will undergo continued development to try and identify optimal conditions for their use. Another Phase II trial suggests that interfering in pathways of T-cell activation with the drug Abatacept (an inhibitor of T-cell co-stimulation) also can be beneficial, and an earlier report had indicated that depletion of B lymphocytes using Rituximab has clear, but transient benefits. Thus, a small arsenal of agents is being identified. Importantly, safety and feasibility in the setting of new-onset disease is becoming established, along with the precedent of enrolling adolescents and children into these studies – important, as new-onset type 1 diabetes is common in this age group.

Antigen-specific immunotherapy

The second approach is termed antigen-specific immunotherapy (ASI). It is well established that induction and restoration of immune tolerance is achieved by administering the very target (autoantigen) against which the destructive autoimmune response is directed. This may seem counter-intuitive and likely to ramp up the autoimmunity; but if the autoantigen is given under appropriate conditions, it seems to work, at least in model systems.

There are different ASI strategies. Using short antigenic peptides representing sequences (epitopes) recognized by T lymphocytes – known as peptide immunotherapy (PIT) – is in Phase I-III development in clinical allergy and

Strategies for halting immune damage to beta cells

- Immune suppression with drugs that inhibit T lymphocyte function
- Immune modulation that promotes a better immune system balance
- Strategies to specifically promote immune regulation in islets
- Combinations of the above

other autoimmune diseases. PIT has several advantages: highly efficient target delivery; avoidance of antibody development; relatively inexpensive synthesis costs; and the fact that the dose is not limited by the biological effects of the parent molecule. In Phase I studies in our centre, it appears safe and well tolerated. Future studies will be needed to evaluate its full potential and the best setting for its deployment.

Alternatively, whole proteins from the beta cell have been used. The lead here is insulin, given orally to first-degree relatives without diabetes who already have islet cell autoantibodies. A clinical study conducted by TrialNet is based on sub-study data that suggest that first-degree relatives who have high titres of anti-insulin autoantibodies might expect particular benefit from this approach in terms of reduced progression to clinical disease. Giving insulin by mouth has no metabolic effect at the dose used but takes advantage of the natural immunological phenomenon that ingested protein antigens are well tolerated by the immune system. The study will report in one or two years and, it is hoped, will provide better understanding of the mechanisms of oral immunological tolerance in humans.

The other advanced drug in the ASI area was the whole beta-cell protein/autoantigen GAD65 (glutamic acid decarboxylase isoform 65 kDa; Diamyd® GAD65). Although promising results (preservation of insulin reserve) were reported in a post-hoc analysis of a subset of cases treated with GAD65-alum prime and boost in 2008, a repeat conducted by TrialNet reported no benefit in 2011. Full reporting of the results of a Phase III study are expected, although preliminary reports suggest no preservation of C-peptide preservation.

What does the future hold for type 1 diabetes therapeutic strategies?

Can sense be made of these ebbs and flows of positive and negative clinical trial data? There is a picture emerging that non-specific, biologic-based therapies are effective when given close to diagnosis, whereas antigen-specific immunotherapy is not – probably because it operates sub-optimally in such an active inflammatory setting. Encouraging data from oral insulin studies suggest that building tolerance against beta-cell autoantigens may be useful if given early and for prolonged periods. Moreover, its excellent safety profile means that administration in at-risk groups is feasible. Future developments for ASI will centre on maximizing this potential, probably using multiple antigens or better delivery systems. New therapeutic modalities at very early stages of evaluation include attempts to bolster immune regulation using the approach of adoptive cell transfer.

It seems probable that, like many complex human disorders of unknown aetiology, type 1 diabetes ultimately may be controlled via a therapeutic approach that combines multiple agents with different modes of action. The advantages of such a strategy include minimizing the toxicities and realizing the synergies that enhance and prolong efficacy. The degree to which non-specific immunotherapy and antigen-specific therapy are combined may need to be different according to the stage of disease, for lower risk in the pre-diabetes setting and higher potency in newly diagnosed people.

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Further reading

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