B-lymphocyte therapy for Type 2 diabetes: the 'B' side of diabetic medication?

"The exciting new findings implicating components of the adaptive immune system now present the possibility of targeting B lymphocytes for Type 2 diabetes."

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Type 2 diabetes is a common chronic metabolic disease that has a strong association with serious long-term health complications. These complications include an overall reduction in life expectancy and an increased risk of cardiovascular disease as well as microvascular complications leading to end-stage organ damage. It is clear that the prevalence of diabetes has reached epidemic proportions. In the USA alone, nearly 26 million people live with diabetes, with the total economic health care costs for treating diagnosed diabetes in the USA estimated to be US$245 billion for 2012 [1]. Similar challenges face both developing and developed nations, driving the search for a better understanding of disease mechanisms and the development of novel treatments.

"Further work to elucidate the involvement of B lymphocytes in the etiology of human Type 2 diabetes will no doubt yield important insights into disease mechanisms and open up novel avenues for therapeutic intervention."

It is becoming increasingly apparent that while Type 2 diabetes (T2D) is a metabolic disease, it has an inflammatory component [2]. It has long been recognized from cross-sectional and prospective studies that T2D patients have demonstrated increased levels of inflammatory factors in the circulation. Further to this, animal studies provide strong evidence for inflammation in insulin-responsive tissues as well as the pancreatic islets of Langerhans [2,3]. There is a powerful correlation between insulin resistance and adiposity [3], and both human and animal studies show that obesity results in an increased accumulation of inflammatory macrophages in adipose tissue, especially the visceral depot [4]. These potent immune cells elaborate inflammatory mediators into the circulation that impact upon insulin action. These findings lend additional support to the notion that an imbalance of pro- and anti-inflammatory adipokines secreted by adipose tissue contributes to metabolic dysfunction [2,3].

B lymphocytes as new players in diabetes

In very recent studies, the concept of inflammation involvement in T2D has been extended to include cells of the adaptive arm of the immune system [2], particularly antibody-producing B lymphocytes. In a seminal study by Winer and colleagues, the effect of B-lymphocyte deficiency upon metabolic outcomes in one animal model of diet-induced obesity was examined [5]. Here it was found that compared with normal mice that exhibited a proinflammatory cytokine profile with insulin resistance and glucose intolerance, B-lymphocyte-deficient mice demonstrated less inflammation in response to obesity and were not insulin-resistant, but exhibited improved glucose tolerance [5]. These studies provide mechanistic support for the observation that B lymphocytes accumulate within the adipose tissues of obese human subjects [6] and the very recent findings that human B cells support the inflammation that may contribute to T2D [7]. Significantly, Winer and colleagues demonstrated that insulin resistance in humans with obesity was associated with specific IgG autoantibodies, whereas the therapeutic depletion of B lymphocytes in their animal model protected against impaired glucose metabolism and increased insulin sensitivity [5]. The notion that T2D has an inflammatory component has supported clinical trials testing the efficacy of anti-inflammatory agents including salsalate and IL-1 blockers, which have demonstrated moderate improvements in glycemic control and increased insulin levels and β-cell function rather than reduced insulin resistance [8,9]; the response to salsalates included

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reduced insulin clearance [8]. The exciting new findings implicating components of the adaptive immune system now present the possibility of targeting B lymphocytes for T2D.

Clinical drug candidates to deplete B lymphocytes in human subjects

The most obvious clinical candidate for such an approach would be the B-lymphocyte-depleting agent rituximab [10], a US FDA-approved chimeric human–mouse monoclonal antibody (mAb) indicated for the treatment of hematological malignancies and autoimmune diseases including CD20-positive B-cell non-Hodgkin's lymphoma, and for refractory rheumatoid arthritis. Other clinical possibilities for B-lymphocyte depletion include targeting the B-lymphocyte trophic factor (BAFF) [11]. Indeed, human anti-BAFF (scFv) mAb LymphoStatB® (belimumab) developed by Human Genome Sciences Inc. (MD, USA) is being tested in a Phase III clinical trial for systemic lupus erythematosus [12], while TACIIg (atacicept) developed by ZymoGenetics Inc. (WA, USA), which can also block BAFF, is under clinical trials in rheumatoid arthritis patients [13]. A Phase IIb clinical trial to evaluate the effects of a mAb against the B-lymphocyte surface protein CD22 (epratuzumab, IMMU-103; Immunomedics Inc., NJ, USA) for systemic lupus erythematosus is now underway [14]. Based on animal studies, other approaches to deplete B lymphocytes may also be available in the future, such as BCMA-Fc, which is capable of blocking both BAFF and APRIL [15]. Nonetheless, major considerations when assessing B-lymphocyte-depleting agents as therapeutics will relate to differences in their kinetics of depletion, the particular B-lymphocyte subsets targeted, their clinical efficacy and their modes of action. In particular, their relative safety profile seen in the context of diabetes versus potential benefits will need to be carefully evaluated.

Past experience with B-lymphocyte depletion for diabetes

Although rituximab has not been used to treat T2D *per se*, it has been tested for diabetes conditions that exhibit a B-lymphocyte involvement. As one example, administration of rituximab has been tested in a rare instance, with a positive outcome, for the type B syndrome of severe insulin resistance [16], a condition caused by circulating antibodies directed against the insulin receptor. In this case, the test subject showed good glycemic control for up to 11 months after initial treatment. A more extensive Phase II trial for subjects with autoimmune Type 1 diabetes (T1D), which also exhibits a B-lymphocyte etiology [17], has been completed [18]. In this trial, treated subjects showed some short-term preservation of β-cell function for up to 1 year post-treatment. Thus, of the possible agents indicated above, only rituximab has been tested in the context of T1D [18].

Reported interactions between rituximab & glucose control

These aforementioned cases support the idea that targeting B lymphocytes may be beneficial for autoimmune forms of diabetes such as T1D [19], but the use of these types of strategies for T2D needs further consideration. Despite the many thousands of people treated with rituximab and the high incidence of T2D in developed nations, there are few reports demonstrating any relationship between rituximab administration and changes in insulin resistance and/or euglycemia. Of particular note, hypoglycemia has been reported as a very rare toxicity of rituximab [20]. The mechanisms for this are unknown, but it is interesting to speculate that this may relate to changes in insulin output, insulin sensitivity and/or glucose disposal rates. These data may indeed draw some parallels with the animal studies whereby B-lymphocyte-deficient rodents placed on a high-fat diet to induce diabetes show improvements in insulin resistance and glucose tolerance [5].

Considerations for B-lymphocyte depletion in subjects with diabetes

There is, at this time, some contention as to whether inflammation is the driving cause of insulin resistance in human subjects or a secondary feature of obesity-induced diabetes [3]. Such a consideration is important when one is considering the potential clinical efficacy of a powerful immune intervention strategy. Indeed, rituximab results in almost immediate and profound B-lymphocyte depletion, although antibody-mediated immunity remains; B-lymphocyte numbers do not return to normal ranges for up to 9 months after administration. The general consensus is that when used as a monotherapy for hematological malignancies and autoimmune diseases, rituximab is well tolerated [18]. Still, rituximab has a range of commonly observed toxicities – the most prevalent include fever, lymphopenia, nausea and neutropenia – with an increase in specific types of infectious events being reported [21]. Further to this, there are some reports that the use of rituximab

after transplantation, that is, when used in combination with immunosuppression, is associated with a high risk of infectious disease and death related to infectious disease [22]. How rituximab will combine with diabetic medications is not known, although in the recent Phase II trial for T1D, treated subjects showed no evidence of severe adverse reactions or infections (grade I or II only) [18]. Still, the verifiable infectious risks associated with rituximab may pose a considerable contraindication for its use as a treatment when considering the potentially large sectors of the population with T2D. Thus, one will need to carefully consider the relative benefits of immune therapy in the context of other available interventions for T2D that clearly improve glucose control such as lifestyle modifications and diabetic medications [23].

Conclusion

In conclusion, exciting new data from animal models of obesity-induced diabetes, as well as some human studies, indicate involvement of B lymphocytes in the development of T2D. These new insights open up the discussion for intervention strategies that target the adaptive B-lymphocyte arm of the immune system for T2D. To date, such approaches have only been trialed for autoimmune T1D where moderate improvements in glucose control have been observed with no evidence of severe adverse reactions or infections after administration of B-lymphocyte-depleting agents [18,19]. Further work to elucidate the involvement of B lymphocytes in the etiology of human T2D will no doubt yield important insights into disease mechanisms and open up novel avenues for therapeutic intervention.

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