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The use of interleukin-1-receptor antagonists in the treatment of diabetes mellitus

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Decreased functional islet [beta]-cell mass is the main cause of onset and progression of both type 1 and 2 diabetes mellitus. In type 1 diabetes mellitus, [beta]-cell death is predominantly due to an autoimmune-driven, T-cell-mediated inflammatory process in the islets.¹ Although the mechanisms of [beta]-cell failure in type 2 diabetes mellitus remain debated, stress and inflammatory pathways have been implicated. For example, metabolic stress caused by repetitive glucose excursions, dyslipidemia and adipokines¹ can induce an inflammatory response characterized by local cytokine secretion,² islet immune-cell infiltration,³ [beta]-cell apoptosis, amyloid deposits, and eventual fibrosis. Thus, islet inflammation could be a shared feature of both types of diabetes mellitus, converging on a common pathway that leads to [beta]-cell secretory failure and apoptosis. In this context, interleukin-1[beta] (IL-1[beta]) has emerged as a master cytokine, which regulates islet chemokine production and causes impaired insulin production and [beta]-cell death.⁴ Preclinical studies of IL-1 antagonism in animal models of both type 1 and type 2 diabetes mellitus have shown promising results.¹ In this Viewpoint, we discuss the potential role of anakinra—a recombinant human IL-1-receptor antagonist—in the treatment of diabetes mellitus.

Anakinra is a competitive inhibitor of IL-1 binding to type I IL-1 receptors.⁵ This agent is currently licensed for the treatment of rheumatoid arthritis unresponsive to other disease-modifying antirheumatic drugs. As IL-1[beta] clearly has a key role in the

pathogenesis of diabetes mellitus, the availability of anakinra allowed us to conduct a clinical trial of IL-1 receptor antagonism in patients with type 2 diabetes mellitus.⁶

In our study, 70 patients were randomly allocated to receive either receive placebo or a subcutaneous injection of 100 mg anakinra once daily for 13 weeks. At study end, the HbA_{1c} level was lower in the anakinra-treated group than in the placebo group (between-group difference 0.46%, 95% CI 0.01–0.90%; $P = 0.03$). Importantly, [beta]-cell secretory function was enhanced by treatment with anakinra and the proinsulin-to-insulin ratio (an indicator of [beta]-cell stress) was reduced. A marked reduction of systemic inflammation as reflected by decreased serum IL-6 and C-reactive protein levels was also observed. Interestingly, however, insulin resistance, insulin-regulated gene expression in skeletal muscle, serum adipokine levels, and BMI were all unaffected. Symptomatic hypoglycemia and other apparent drug-related serious adverse events were not observed, in line with the well-documented favorable safety profile of IL-1 antagonism in patients with rheumatoid arthritis. Our study, therefore, represents the first proof-of-principle that IL-1 antagonism has therapeutic potential in the treatment of diabetes mellitus.

Levels of acute-phase proteins are elevated in patients with type 2 diabetes mellitus and chronic low-grade inflammation might play a pathogenetic role in this condition.^{1,7} Elevated levels of IL-1[beta] and IL-6 confer an increased risk for developing type 2 diabetes mellitus.⁸ Many studies have demonstrated an association between markers of systemic inflammation and insulin resistance (but not insulin secretion).⁷ Unfortunately, however, intervention studies targeting TNF, IL-6 and IL-1 by specific antibodies or receptor antagonism have failed to show any effect on insulin resistance.^{1,6} Possibly, circulating cytokines might origin predominantly from

inflammatory lesions in the vessel wall and may not reflect the activity of the inflammatory process in adipose tissues. It should be noted, however, that cytokines act in networks, and that implementation of a more-potent inhibition or production of a general inflammatory blockade by antagonization of several cytokines could be needed to affect insulin sensitivity. Nonetheless, the marked decrease in systemic inflammation observed with anakinra could represent an added treatment benefit for cardiovascular disease associated with diabetes mellitus. The effects of anakinra on cardiovascular disease will, therefore, be assessed in future studies.

The clinical relevance of our trial has been questioned because of the seemingly modest change in HbA_{1c} levels. Anakinra has a short half-life of 4–6 h and is a weak antagonist that requires a 500-fold molar excess to block IL-1 action. As the patients enrolled in our study were overweight or obese (BMI >27 kg/m²), it is likely that they were under dosed. The FDA-approved dose of anakinra for rheumatoid arthritis is 100 mg per day and so was the only dose ethically justifiable for this proof-of-concept study. Accordingly, changes in HbA_{1c} levels in anakinra-treated patients correlated negatively with baseline BMI and body surface area as surrogates of anakinra drug-distribution volume.

When patients in our study were stratified into tertiles according to body surface area, the improvement in HbA_{1c} was 0.84% in the lowest tertile, comparable to that observed with glucagon-like peptide-1-based therapies. Notably, a 1% absolute reduction in the HbA_{1c} level is associated with a 21% lower relative risk for developing late diabetic complications.⁹ Dose-escalation could, therefore, result in a clinically meaningful reduction in HbA_{1c} levels in very obese patients. The patients included in our study had long-term duration of diabetes mellitus, and most were treated with oral

antidiabetic agents alone or in combination with insulin. Drug-naïve patients with recent onset of disease might, therefore, benefit more from treatment with anakinra.

Can the improved glycemia caused by IL-1 antagonism be explained by a discrete change in insulin sensitivity undetectable by euglycemic hyperinsulinemic clamp? For example, an improvement in hepatic insulin sensitivity offset by a worsening of insulin action in muscle, resulting in an increment in [beta]-cell function. It is difficult to envisage how unchanged whole-body insulin sensitivity would physiologically signal an increased [beta]-cell secretory response and so lead to an appreciable reduction in glycemia. Furthermore, anakinra markedly improved the proinsulin-to-insulin ratio, did not change insulin-regulated gene expression in skeletal muscle, and did not affect the levels of circulating adipokines. Several lines of evidence from our study, therefore, clearly support a direct improvement of [beta]-cell secretory function by anakinra.

Increased apoptosis is the major defect that leads to decreased [beta]-cell mass in patients with diabetes mellitus.¹⁰ Novel therapeutic approaches designed to inhibit cell death could be a key development in the management of diabetes mellitus, possibly in combination with agents with [beta]-cell regenerative potential such as glucagon-like peptide-1. Rather than just palliate glycemia, IL-1 antagonism might represent a novel and realistic treatment principle directed against the causal pathogenetic processes that underlie diabetes mellitus, whereby the progressive decline in functional [beta]-cell mass, insulin resistance and angiopathy could be prevented or even reversed. IL-1 antagonism has potential as a disease-modifying agent in diabetes mellitus. Although the autoinflammatory feature of type 2 diabetes mellitus might be successfully antagonized by targeting IL-1[beta] alone, the autoimmune component of type 1 diabetes mellitus could require combination therapy (e.g. with anti-CD3 antibodies).

Future studies should also evaluate the clinical benefit of IL-1 antagonists with prolonged half-lives that allow weekly or monthly injection schedules.

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