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Is anti-inflammatory therapy for type 2 diabetes mellitus ready for routine clinical practice?

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Abstract

BACKGROUND—Type 2 diabetes mellitus (T2DM) is characterized by a progressive loss of pancreatic function, which results in part from increased β -cell apoptosis. The inflammatory cytokine interleukin 1 β (IL-1 β) is a putative mediator of apoptosis in this context.

OBJECTIVE—To evaluate the efficacy of a recombinant IL-1-receptor antagonist (anakinra) as a novel therapy for T2DM.

DESIGN AND INTERVENTION—This was a 13-week, double-blind, placebo-controlled study of anakinra in adults with T2DM. Inclusion criteria included age ≥ 20 years, disease duration > 3 months, HbA_{1c} level $> 7.5\%$, BMI > 27 kg/m², and stable medication in the 3-month period before enrollment. Exclusion criteria included autoantibody-positivity, HbA_{1c} $> 12\%$, fasting C-peptide level < 0.400 nmol/l, current use of anti-inflammatory agents, infection, neutropenia, anemia, liver or renal disease, cancer, and immunodeficiency. Eligible participants were randomly allocated to receive 100 mg anakinra or placebo, self-administered by subcutaneous injection every morning. All other antidiabetic medications or lifestyle interventions remained unchanged. A 2 h oral glucose tolerance test was performed at baseline and week 13 to assess the levels of glucose, proinsulin, insulin, and C-peptide. Insulin sensitivity was assessed by euglycemia–hyperinsulinemia clamp analysis and insulin-regulated gene expression was determined from skeletal muscle biopsies.

OUTCOME MEASURES—The primary outcome measure was the change from baseline in HbA_{1c}. Secondary outcome measures included β -cell function, insulin sensitivity, insulin-regulated gene expression, and the levels of adipokines and inflammatory markers.

RESULTS—A total of 34 patients received anakinra. The placebo group comprised 35 patients, 2 of whom withdrew before study end. The mean HbA_{1c} level at baseline was 8.7% in the anakinra group and 8.2% in the placebo group. By week 13, the mean HbA_{1c} level was reduced by 0.33% in the anakinra group but was increased by 0.13% in the placebo group. The between-group difference in the mean HbA_{1c} level was 0.46% (95% CI 0.01–0.90%, $P = 0.03$). Overall, 61.8% of patients in the anakinra group experienced a reduction in HbA_{1c}, compared with only 30.3% of patients in the

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Competing interests

JL Nadler has declared associations with the following companies: DiaKine Therapeutics, Merck and Novartis. See the article online for full details of the relationship. The other authors declared no competing interests.

placebo group ($P < 0.001$). The effect of anakinra on the HbA_{1c} level was apparent from 4 weeks of treatment ($P = 0.004$). When compared with placebo, the ratio of proinsulin to insulin was lower in the anakinra group ($P = 0.005$). In addition, C-peptide secretion was enhanced ($P = 0.04$) in the anakinra group. Treatment with anakinra was also associated with reduced levels of inflammatory markers and decreased neutrophil and platelet counts. By contrast, there were no significant differences between the groups in BMI, insulin sensitivity, insulin-regulated gene expression, or adipokine levels. Transient injection-site reactions were reported by 17 patients in the anakinra group.

CONCLUSION—Treatment with anakinra reduced inflammation and improved β -cell function and glycemic control of patients with T2DM.

Keywords

anakinra; β cell; glycemic control; interleukin 1 β ; type 2 diabetes mellitus

COMMENTARY

The underlying defect in T2DM is more complex than insulin resistance associated with increased visceral adiposity. The United Kingdom Prospective Diabetes Study established a connection between declining β -cell function and progression of T2DM, which implies a progressive defect in insulin secretion, as well as insulin resistance. In addition, histological evidence has implicated β -cell dysfunction (manifesting as loss of β -cell mass) in the elevated fasting blood glucose concentration typical of T2DM.¹

A link between T2DM and inflammation has also been proposed. This hypothesis is supported by observations of macrophage infiltration into the pancreas,² increased β -cell apoptosis,³ and the association between T2DM and atherosclerosis. The mechanisms that trigger inflammatory damage to pancreatic β cells are not well understood, but probably involve the interplay between environmental and genetic factors, which leads to immune-mediated inflammatory cytokine release. Cytokines implicated in this process include IL-1 β , IL-6, IL-8, IL-12, and tumor necrosis factor.

IL-1 β is thought to mediate proinflammatory pathways in multiple diseases, including diabetes mellitus. IL-1 β binds to the IL-1 receptor, which leads to activation of the proapoptotic transcription factor nuclear factor κ B, DNA fragmentation, and impaired β -cell function.³ Studies suggest an autocrine role for IL-1 β in damage to rodent and human islets; however, some results in human islets have cast doubt on the autocrine role of IL-1 β in β -cell toxicity in T2DM.⁴ The naturally occurring competitive antagonist of IL-1 β (IL-1ra) binds to the IL-1 receptor without subsequent activation of the nuclear factor κ B signaling pathway. IL-1ra quenches the systemic inflammatory response induced by IL-1 β . Genetic variants in the IL-1ra gene have been associated with a number of complications of diabetes mellitus, such as stroke and renal disease.⁵

Larsen *et al.* report the results of a small, 13-week study of the recombinant interleukin-1-receptor antagonist anakinra for the treatment of T2DM. The results on glycemic control and β -cell function using a fixed dose of anakinra are encouraging, although not yet sufficiently compelling to alter clinical practice. Efficacy was modest: by week 13 the levels of HbA_{1c} had declined by 0.33% in the anakinra treatment group. Of note, the effect of anakinra on HbA_{1c} was less pronounced at 13 weeks than at 4 weeks of treatment. Long-term safety issues remain unaddressed. Furthermore, inflammatory pathways in diabetes mellitus are diverse and complex—blocking the effect of a single cytokine might not yield robust β -cell protection.

Although the role of systemic inflammation in insulin resistance is clear, the role of islet inflammation in T2DM is not well defined. The therapy described by Larsen *et al.* is obviously

not ready for routine clinical practice; however, their study breaks new ground as it provides evidence to suggest that islet inflammation could be a key component in the pathophysiology of T2DM. Most current treatments for T2DM focus on prevention and mitigation of complications primarily through glycemic control, which often requires therapy escalation because of reduced effectiveness over time. Currently available therapies have not demonstrated an ability to preserve β -cell function and mass. Immunomodulatory anti-inflammatory agents might, therefore, provide exciting new disease modifying treatments for T2DM.

In conclusion, the data presented by Larsen *et al.* warrant follow-up and longer-term investigation to determine whether agents that modulate local inflammatory cytokines in islets represent the next generation of mechanistically targeted therapeutic agents for T2DM.

PRACTICE POINT

Anakinra improved multiple metabolic parameters of type 2 diabetes mellitus, although the overall effect on glycemic control was modest; nonetheless, this study introduces a novel concept in targeted anti-inflammatory drug therapy

References

1. Ritzel RA, et al. Relationship between β -cell mass and fasting blood glucose concentration in humans. *Diabetes Care* 2006;29:717–718. [PubMed: 16505537]
2. Ehses JA, et al. Increased number of islet-associated macrophages in type 2 diabetes. *Diabetes* 2007;56:2356–2370. [PubMed: 17579207]
3. Maedler K, et al. Glucose-induced β cell production of IL-1 β contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* 2002;110:851–860. [PubMed: 12235117]
4. Welsh N, et al. Is there a role for locally produced interleukin-1 in the deleterious effects of high glucose or the type 2 diabetes milieu to human pancreatic islets? *Diabetes* 2005;54:3238–3244. [PubMed: 16249450]
5. Worrall BB, et al. IL1RN VNTR polymorphism in ischemic stroke: analysis in 3 populations. *Stroke* 2007;38:1189–1196. [PubMed: 17332449]

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