Thomas Mandrup-Poulsen

Interleukin-1 Antagonism: A Sturdy Companion for Immune Tolerance Induction in Type 1 Diabetes?

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Intervention trials testing immunomodulatory monotherapies in type 1 diabetes have generally been disappointing (1). Possible explanations include suboptimal pharmacokinetics/dynamics or inappropriate dosing/timing of the interventions and heterogeneity of study populations. However, considering that β-cell destruction in type 1 diabetes involves complex cooperation between the innate and adaptive immune systems (2), evolutionarily designed to provide foolproof protection of the host with redundant backup systems against environmental threats, we have been naïve in our belief that monotherapies would cure type 1 diabetes.

Although combination therapy for type 1 diabetes may increase efficacy and safety, clinical testing of drug combinations is a daunting enterprise. How do we decide on rational and safe combinations, doses, timing, and in which patients? How do we obtain regulatory approval, funding, and sufficient statistical power with the limited number of available patients? Is there solid preclinical evidence favoring a certain combination?

Animal models of type 1 diabetes have been rightly mocked for unjustified promise for prevention (3,4). However, few animal studies have shown reversal of overt diabetes (5), and therefore it is worth paying attention to these studies because of their relevance to the treatment not of at-risk patients, but of patients with disease of recent onset. In this issue, Pagni et al. (6) report one of these rare studies using transgenic mice with β-cell–specific expression of lymphocytic choriomeningitis virus in which diabetes is induced acutely by infecting the mice with the virus and thereby triggering an autoimmune response against the β-cells that express viral antigens. Interestingly, they report that intraperitoneal injection once weekly for 4 weeks with antibody against the key innate immune mediator interleukin-1β (IL-1β) potentiated the partial reversal of diabetes obtained by tolerizing immunization with the β-cell antigen GAD65, given as intramuscular DNA plasmid injections on days 0, 4, and 11 after disease onset.

Pagni et al. confirms the markedly potentiating effect of IL-1 antagonism on the partial reversal of autoimmune diabetes in the NOD mouse model obtained by administration of a deliberately suboptimal dose of a nondepleting antibody against the common T lymphocyte marker cluster of differentiation (CD) 3, which induces immune tolerance in recipient mice (7). In both studies, IL-1 antagonism alone caused no or insignificant reversal. The novelty of the study by Pagni et al. is that IL-1 antagonism potentiated β-cell antigen–specific tolerance induction. One strength of the article is its careful data analysis. Subjective stratification on baseline glucose using 400 mg/dL as surrogate threshold for β-cell function revealed that efficacy of the combination therapy was restricted to animals with glycemia below that threshold. More imaginatively, when analyzing noncured animals, combination therapy conferred milder and nonprogressive hyperglycemia.

A weakness of the studies by Pagni et al. (6) and Ablamunits et al. (7) is their lack of clear understanding of the mechanism of action by which IL-1 antagonism potentiates tolerance induction. IL-1 is believed to counteract immune-tolerance mainly by reducing differentiation of adaptive regulatory T cells, by costimulating antigen-specific proinflammatory T-cell helper (Th)1 and Th17 cell activation (8–11) and by stimulating target tissue immune infiltration by chemokine induction (8,12,13). Consistent comparisons between placebo-, mono-, and

Immuno-endocrinology Laboratory, Section for Endocrinological Research, Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; and Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Corresponding author: Thomas Mandrup-Poulsen, tmpo@sund.ku.dk.

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combination-arms allowed Ablamunits et al. (7) to propose that IL-1 antagonism synergizes with the anti-CD3–mediated increase in regulatory T cells and a Th1 to Th2 conversion by upregulating anti-inflammatory IL-10 production, possibly inducing a pro- to anti-inflammatory shift in the splenic CD11b/c^{+} macrophage/dendritic cell phenotype. Although the number of these cells was unaffected, the proportion of CD11b/c^{+} cells with an anti-inflammatory phenotype evidenced by the expression of arginase-1, an enzyme that breaks down L-arginine to urea, was increased by IL-1 antagonism alone and in combination. This may promote immune tolerance by preventing autoantigen presentation. This may also protect target β-cells from direct IL-1–mediated damage because IL-1 potently induces expression of β-cell inducible nitric oxide synthase (iNOS), an enzyme that generates toxic nitric oxide (NO) from conversion of L-arginine to -citrulline, and also reduces β-cell arginase-1 expression (14–16). IL-1 antagonism thus would effectively block NO production by preventing iNOS expression and the availability of its substrate. This effect may explain the stunning rapidity of disease reversal observed (100% cure using IL-1β antibody and increased pancreatic insulin contents within 1 week post therapy), as it would be dependent on restoration of β-cell function, with restoration of mass expected to occur much later.

In the study by Pagni et al., the mechanisms of action underlying IL-1 antibody synergy with GAD tolerance induction are more difficult to tease apart because placebo and IL-1 antibody monotherapy comparisons are only carried out in a limited number of investigations. The contribution of GAD immunization was to reduce islet immune infiltration, likely by modestly increasing regulatory T cells and reducing splenic cytotoxic T-cell activity determined by their tumor necrosis factor (TNF) and interferon-γ production. IL-1 antibody alone had no effects on these parameters, but did synergize with GAD immunization in reducing pancreatic lymph node helper T cell IL-2 and cytotoxic T-cell TNF production. More strikingly, IL-1 antibody reduced the number of islet CD11b$^{+/high}$ and cytotoxic T cells. The CD11b$^{+/high}$ cells were not further phenotyped, in particular regarding arginase expression.

Thus, the mechanistic studies, incomplete as they are, suggest that IL-1 antagonism contributes to the tolerizing synergy primarily by reducing recruitment and/or activation of islet CD11b$^{+/high}$ macrophages, whereas anti-CD3 antibody or islet antigen immunization contributes mainly by T-cell regulation, jointly leading to reduced intraislet inflammation and expression of cytotoxic inflammatory mediators (Fig. 1).

The studies by Pagni et al. (6) and Ablamunits et al. (7) have considerable clinical relevance as human trials have demonstrated that anti-CD3 therapy (17) or DNA plasmid-conveyed antigen-specific proinsulin tolerization (18) each transiently or partially improved β-cell function in recent-onset type 1 diabetic patients, and that although IL-1 antagonism as monotherapy was ineffective, it was safe (19). Therefore, there is now both a preclinical and clinical rationale to warrant human trials of the combination of IL-1 antagonism with antigen-specific or nonspecific adaptive immune modulations in type 1 diabetes of recent onset.

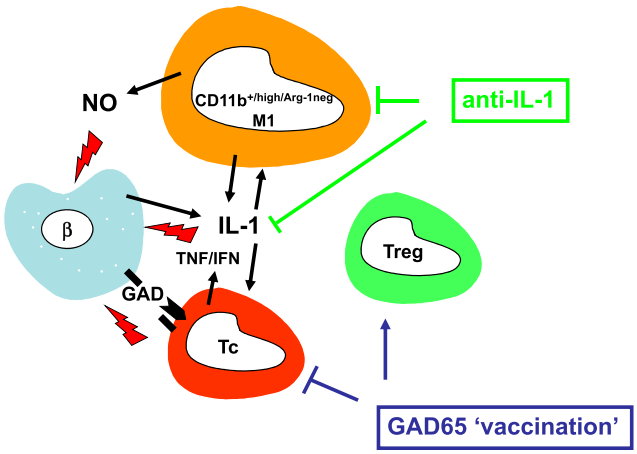

Figure 1—Model of the mechanisms by which IL-1 antagonism (anti-IL-1) and GAD "vaccination" each contribute to synergize in tolerance induction in type 1 diabetes of recent onset. IL-1 antagonism reduces the recruitment and/or activation of islet CD11b$^{+/high/Arg-1neg}$ proinflammatory M1 macrophages. GAD vaccination induces regulatory T cells (Treg), leading to reduced activation and recruitment of cytotoxic T cells. Jointly M1- and T-cell regulation reduces intraislet inflammation and expression of β-cell cytotoxic inflammatory mediators IL-1, TNF-α, interferon-γ (IFN), and NO. Arg-1, arginase-1; Tc, cytotoxic T cell.

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References

1. Mandrup-Poulsen T. Perspective: testing failures. Nature 2012;485:S17
2. Mandrup-Poulsen T, Pickersgill LMS, Donath MY. Blockade of interleukin 1 in type 1 diabetes mellitus. Nat Rev Endocrinol 2010;6:158–166
3. Atkinson MA, Leiter EH. The NOD mouse model of type 1 diabetes: as good as it gets? Nat Med 1999;5:601–604
4. Roep BO, Atkinson M, von Herrath M. Satisfaction (not) guaranteed: re-evaluating the use of animal models of type 1 diabetes. Nat Rev Immunol 2004;4:989–997
5. Kachapati K, Adams D, Bednar K, Ridgway WM. The non-obese diabetic (NOD) mouse as a model of human type 1 diabetes. Methods Mol Biol 2012;933:3–16
6. Pagni PP, Bresson D, Rodriguez-Calvo T, et al. Combination therapy with an anti–IL-1β antibody and GAD65 DNA vaccine can reverse recent-onset diabetes in the RIP-GP mouse model. Diabetes 2014;63:2015–2025
7. Ablamunits V, Henegariu O, Hansen JB, et al. Synergistic reversal of type 1 diabetes in NOD mice with anti-CD3 and interleukin-1 blockade: evidence of improved immune regulation. Diabetes 2012;61:145–154
8. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 2011;117:3720–3732
9. Bertin-Maghit S, Pang D, O'Sullivan B, et al. Interleukin-1β produced in response to islet autoantigen presentation differentiates T-helper 17 cells at the expense of regulatory T-cells: implications for the timing of tolerizing immunotherapy. Diabetes 2011;60:248–257

10. Ben-Sasson SZ, Hu-Li J, Quiel J, et al. IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and differentiation. Proc Natl Acad Sci U S A 2009;106:7119–7124
11. O'Sullivan BJ, Thomas HE, Pai S, et al. IL-1 beta breaks tolerance through expansion of CD25+ effector T cells. J Immunol 2006;176:7278–7287
12. Steer SA, Scarim AL, Chambers KT, Corbett JA. Interleukin-1 stimulates beta-cell necrosis and release of the immunological adjuvant HMGB1. PLoS Med 2006;3:e17
13. Eizirik DL, Sammeth M, Bouckenooghe T, et al. The human pancreatic islet transcriptome: expression of candidate genes for type 1 diabetes and the impact of pro-inflammatory cytokines. PLoS Genet 2012;8:e1002552
14. Modolell M, Corraliza IM, Link F, Soler G, Eichmann K. Reciprocal regulation of the nitric oxide synthase/arginase balance in mouse bone marrow-derived macrophages by TH1 and TH2 cytokines. Eur J Immunol 1995;25:1101–1104
15. Cunningham JM, Mabley JG, Green IC. Interleukin 1beta-mediated inhibition of arginase in RINm5F cells. Cytokine 1997;9:570–576
16. Stickings P, Mistry SK, Boucher JL, Morris SM, Cunningham JM. Arginase expression and modulation of IL-1beta-induced nitric oxide generation in rat and human islets of Langerhans. Nitric Oxide 2002;7:289–296
17. Daifotis AG, Koenig S, Chatenoud L, Herold KC. Anti-CD3 clinical trials in type 1 diabetes mellitus. Clin Immunol 2013;149:268–278
18. Roep BO, Solvason N, Gottlieb PA, et al. Plasmid-encoded proinsulin preserves C-peptide while specifically reducing proinsulin-specific CD8+ T cells in type 1 diabetes. Science Transl Med 2013;5:191ra182
19. Moran A, Bundy B, Becker DJ, et al.; Type 1 Diabetes TrialNet Canakinumab Study Group; AIDA Study Group. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. Lancet 2013;381:1905–1915