of the 43% reduction in CSDD scores in the placebo group in that time. If waiting is too distressing for patients or their families, the next step of psychosocial interventions could occur sooner.

Evidence of improvement in rates and severity of depression exists for several community based-interventions involving carers of people with Alzheimer's disease: carer-given problem solving therapy or pleasurable events schedules;[9] exercises and carer-given behaviour management therapy;[10] interpersonal therapy;[11] or occupational therapist training in compensatory and environmental strategies combined with cognitive behavioural therapy provided to carers.[12]

The HTA-SADD trial[1] does not advocate abandonment of antidepressants in people with Alzheimer's disease and depression. Anecdotally, clinicians report successful treatment of patients with antidepressants. Therapeutic trials for individual patients are warranted, although not as first-line treatment unless depression is severe. Antidepressants might have benefits to other psychiatric symptoms secondary to dementia, as indicated by reports that hallucinations, delusions, and agitation benefit from citalopram.[13] Finally, there are anecdotal accounts of use of electroconvulsive therapy in severe depression.

The HTA-SADD trial[1] has underscored the need for clinicians to think about creative alternatives to drug treatment for management of depression in people with dementia, and to use evidence-based techniques and partnerships with family carers.

Henry Brodaty
Brain and Ageing Research Program and Primary Dementia Collaborative Research Centre, School of Psychiatry, Faculty of Medicine, University of New South Wales, NSW 2052, Australia
h.brodaty@unsw.edu.au

I declare that I have no conflicts of interest.

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New hope for immune intervention therapy in type 1 diabetes

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See Articles page 412

In the wake of disappointing results from the first phase 3 immune intervention trials in type 1 diabetes mellitus, a report by Tihamer Orban and colleagues in *The Lancet*[1] could provide a much desired glimmer of hope that the course of disease progression can be altered by immunotherapy after all. Treatment of patients with recent-onset type 1 diabetes for 2 years with abatacept (CTLA4 immunoglobulin fusion protein), believed to interfere with priming and activation of T cells, effectively delayed loss of β-cell function for 9 months. This protective effect was preserved for the complete period of 2 years' therapy. This trial is yet another important deliverable from the international Diabetes TrialNet Consortium,[2] which has an impressive efficiency in designing and executing clinical immune intervention trials in type 1 diabetes with swift recruitment of eligible patients.

Cytotoxic T-lymphocyte antigen 4 (CTLA4) is an essential negative regulator of T-cell immune responses (figure). T cells need a co-stimulatory signal in addition to the main antigen-driven signal. Abatacept modulates co-stimulation and prevents full T-cell activation. Conversely, blockade of CTLA4 by ipilimumab augments T-cell activation and proliferation and improved overall survival in a phase 3 study in patients with metastatic melanoma.[3] Because T-cell autoimmunity is pivotal

in the immunopathogenesis of type 1 diabetes, the idea that abatacept could intervene in the spreading of the T-cell repertoire involved in β-cell destruction is attractive and conceivable. However, in the context of new-onset type 1 diabetes, which represents the final stage in the autoimmune β-cell destruction process, this drug would not seem the most obvious candidate for intervention therapy. Its (temporary) efficacy in an immunologically primed context, as in type 1 diabetes, is therefore surprising because abatacept treatment is believed to be ineffective in countering an established immune response, such as allograft rejection. The loss of effectiveness (loss of β-cell function is delayed by about 9 months, but afterwards the slope of decrease in β-cell function becomes similar to that in patients given placebo, despite continued therapy) in the latest TrialNet study seems to underscore this notion, implying that abatacept does not qualify as monotherapy in type 1 diabetes.[4] Yet the legacy of glycaemic control resulting from preserved β-cell function and insulin reserve should not be underestimated. Even temporarily improved glycaemic control delays development and progression of diabetic complications for many years.[5]

Earlier this year, new insight was gained into the mode of action of CTLA4 in negative immune regulation.[6] CTLA4 captures its ligands from opposing cells by transendocytosis. After removal, these co-stimulatory ligands are degraded inside cells expressing CTLA4, resulting in impaired co-stimulation via CD28. How abatacept might act in concert with this regulation pathway, rather than interfere with natural immune regulation acting through CTLA4 triggered internalisation of CD80 and CD86, is difficult to reconcile.

The slope of decrease and the rate of β-cell protection are similar to those seen with other candidate immune modifying strategies (anti-CD3, anti-CD20, and GAD65 vaccination[7]) with a particularly strong effect early in the disease and shortly after therapy, which fades afterwards. Orban and colleagues favour the interpretation that spreading of T-cell responses at that time has decreased, but this explanation would not account for the similarities between the different immunotherapies, raising the question of whether the decrease in β-cell function several months after disease manifestation might be caused by factors other than from the immune system, such as β-cell distress and exhaustion, which might require treatment other than immune intervention.

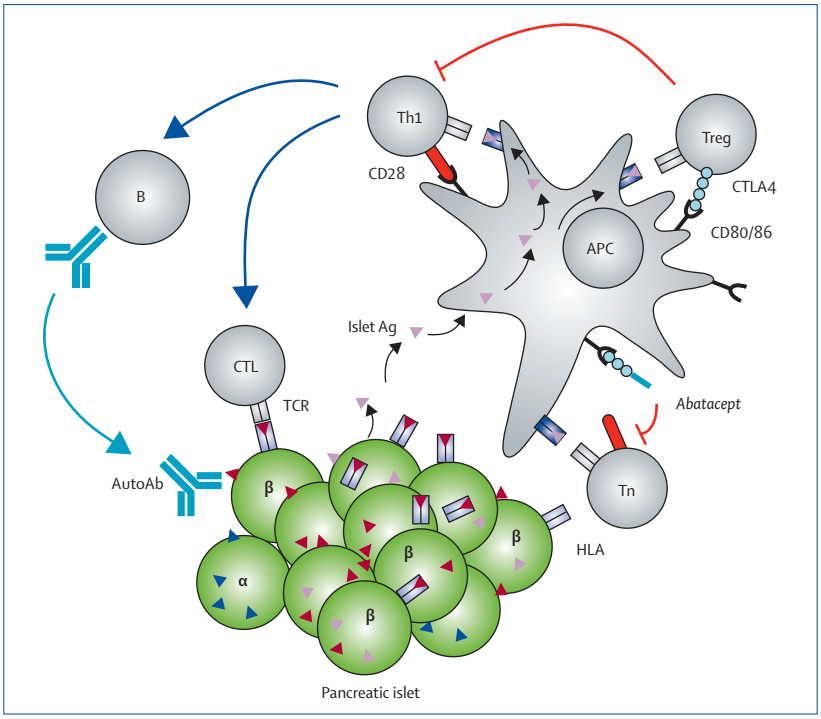

Figure: **Role of co-stimulation in immunopathogenesis and immune intervention in type 1 diabetes**
β-cell proteins are taken up by antigen-presenting cells (APC) and presented by HLA molecules to the immune system. Naive autoreactive T cells (Tn) recognise that these proteins could be primed to become proinflammatory effector T cells (Th1) through co-stimulation by CD28 on T cells with CD80 or CD86 on APC. Effector Th1 cells orchestrate cascade of autoimmune responses that include activation of B cells to produce islet autoantibodies and cytotoxic T cells to lyse β cells expressing islet autoantigen. Once T cells have become activated, they become less dependent on co-stimulation. Regulatory T cells (Tregs) engage co-stimulatory molecule CTLA4 endorsing negative immune regulation to inhibit immune effector T cells. Modulation of co-stimulation via CTLA4 by abatacept interferes with priming of naive T cells through competition with CD28. This could prevent priming of naive T cells and avoid spreading of autoimmune response and progression of disease. Conversely, blockade of CTLA4 with antibody represses regulatory T cells and promotes proinflammatory T-cell responses.

Clinical assessment of immune intervention therapies in type 1 diabetes has had its ups and downs. Initiatives for late prevention studies in patients who are prediabetic failed to delay disease progression,[8] whereas other strategies in patients with recent-onset type 1 diabetes pointed to efficacy when given early after diagnosis, offering hope for patients.[7] Yet hope is an unsafe friend. In view of some disappointing results from phase 3 immune intervention trials in type 1 diabetes that failed to meet their primary endpoints, particular care seems warranted to avoid raising false expectations among patients and physicians.

Type 1 diabetes might represent a heterogeneous disease, in which therapeutic efficacy could differ between patients. The seemingly (the subgroup was small) adverse effect of abatacept in non-white patients in Orban and colleagues' trial warrants further investigation. To define disease activity, progression,

and intervention, there is a great need for discovery and evaluation of biomarkers of insulitis, β-cell function and mass, mechanism of action, immunological and clinical efficacy, and safety, which can act as indicators of disease heterogeneity and differential efficacy of intervention therapy.[9] Even glycated haemoglobin A_{1c}—the present standard for glycaemic control that guides insulin therapy—is a rather heterogeneous surrogate of mean blood glucose.[10]

Despite setbacks in validation of clinical efficacy of immune intervention strategies, Orban and colleagues' study underscores that the future treatment of type 1 diabetes will probably involve immunotherapy, supplementary to treatment of insulin deficiency. To retain steady progress, future studies should appreciate disease and patients' heterogeneity, and include mechanistic studies and monitoring of better correlates of disease progression and preservation of β-cell function and mass. After all, patients with type 1 diabetes have great and unmet medical needs.

Bart O Roep
Department of Immunohaematology and Blood Transfusion, Leiden University Medical Center, Leiden NL-2300RC, Netherlands
boroep@lumc.nl

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Scaling up breastfeeding in developing countries

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See Articles page 420

Early and exclusive breastfeeding is widely regarded as an important intervention that reduces neonatal, infant, and child mortality, and remains a basis for child survival strategies. Breastfeeding is also associated with improved maternal recovery post partum and reduced incidence of diabetes and cancers. As much as 13% of all deaths of children younger than 5 years could be prevented by promotional strategies to increase breastfeeding rates.[1] Subsequent analyses of an assessment of risks associated with partial or no breastfeeding suggested that promotion of breastfeeding could lead to a 11·6% reduction in the number of infant deaths and avert 21·9 million disability adjusted life years (8·6%).[2]

These child mortality estimates were derived from a range of studies, largely small or moderate-sized trials[2] and observational studies[3] that linked early initiation of breastfeeding with neonatal and infant mortality. Meta-analyses[2] suggested that group counselling to promote breastfeeding was associated with increased odds of exclusive breastfeeding in the neonatal period by a factor of 3·9 (95% CI 2·1–7·2, random effects model) compared with routine care and by a factor of 5·2 (1·9–14·2) at 6 months compared with routine care. By contrast, individual counselling was estimated to raise the probability of exclusive breastfeeding in the neonatal period by a factor of 3·5 (2·2–5·4) and by a factor of 1·9 (1·2–3·2) at 6 months compared with routine care. Other research[4] has suggested that prenatal intervention also has a substantial effect on exclusive breastfeeding rates at 12 weeks.

The key issues for nutrition and reproductive health interventions are delivery strategies and platforms, and admittedly experience of scaling up in community-level programmes is limited. Although the outcomes with facility-based interventions are clear,[5] few studies of community interventions assess how promotion