

Can restoring immune balance be the ultimate therapy for type 1 diabetes?

Insulin replacement therapy, which includes multiple daily doses of short-acting and long-acting insulin analogs, insulin pump, continuous glucose monitoring (CGMS), and insulin pump with CGMS, has made a marked advance in the management of type 1 diabetes, of which there is no cure yet. The insulin pump with CGMS, with a warning of hyper- and hypoglycemia, has become available. Achieving near-normal glucose control and reduced rates of severe hypoglycemia are feasible. Despite continuous improvement in insulin therapy, and dedication and scrutiny of both patients and caregivers, treatment targets are not achieved in most patients. Even the most advanced insulin delivery technologies do not replace the capabilities of native insulin-producing β -cells. Under even such technologies, patients with type 1 diabetes required the skill to integrate various factors, such as insulin dose, timing of insulin injection, duration of insulin action, physical activity, seasonal effects, effects of menstruation in women and so on. Transplantation of the pancreas or pancreas/kidney might be the ultimate therapy; however, there are some reports of redevelopment of type 1 diabetes even after the transplantation, and adverse events caused by immune suppressants.

The maintenance of even partial β -cell function has consistently been shown to improve glucose control, and reduce severe hypoglycemia and the rates of secondary end-organ complications. It has been well known that type 1 diabetes results from the destruction of β -cells by self-reactive T cells

that have escaped central and peripheral tolerance¹. Therefore, to arrest the progression of β -cell destruction remains the ultimate target in managing this condition of partial β -cell function. This will hopefully be a treatment for the redevelopment of type 1 diabetes after the transplantation.

There is a need for safe intervention to preserve β -cell function, even if it can reduce hypoglycemia, and improve short- and long-term outcomes. Furthermore, such an intervention needs to have sustained effects without the risk of chronic immune suppression.

The past decades have seen a surge in attempts to do so, with varying degrees of success². However, we know of several side-effects (nephrotoxicity with cyclosporin virus reactivation with high-dose otelexizumab, temporary infertility and alopecia after autologous hematopoietic stem cell therapy).

The immune cells that are thought to cause the destruction of β -cells reside in the effector and memory subsets of CD4 and CD8 T cells. These cells, particularly the effector memory T cells, express CD2. Therefore, a logical strategy to treat type 1 diabetes was to eliminate CD2 T cells with the LFA3 fusion molecule, alefacept, which binds CD2 and results in elimination of T cells expressing this molecule. Alefacept interrupts CD2-mediated T cell costimulation and depletes T cells through a natural killer cell-dependent mechanism³. However, the effect of eliminating these T cells on the disease course was unclear until Rigby's study⁴, because studies with other immune modulators successful in preserving β -cell function did not eliminate antigen-specific T cells.

First of all, Rigby *et al.*⁴ presented the 52-week result of a multicenter, randomized, placebo-controlled, phase 2 trial of

alefacept in new-onset type 1 diabetes (T1DAL). The study protocol of T1DAL was as follows: participants received alefacept (two 12-week courses of 15 mg intramuscularly per week, separated by a 12-week pause). The investigators showed that the frequency of CD4 and most CD8 memory cells was reduced. CD8 effector memory cells are sources interferon- γ , which is involved in β -cell destruction. The investigators noted a significant improvement in the 4-h C-peptide area under the curve (AUC) response to a mixed meal, and the decrease of daily insulin use and the rate of hypoglycemic events. However, the mean glycated hemoglobin at 52 weeks was not different between the alefacept group and the placebo group. The evidence strongly supports the clinical efficiency of this treatment strategy in the first year after diagnosis. In addition, adverse events were infrequent and not severe. The evidence also strongly supports the safety and tolerability of alefacept treatment. The T1DAL trial is the first demonstration that it is possible to specifically and effectively deplete memory T cells in new-onset type 1 diabetes including the CD4 effector memory T cell panel.

Rigby *et al.*⁵ showed the following 52-week result in the middle of 2015, which is another 52-week result after the administration of alefacept. The participants of the T1DAL trial were the same as the previous trial⁵. None of the trial participants were lost. The administration of alefacept was on the two courses of the first paper of T1DAL⁴. End-points were assessed at 104 weeks, and included meal-stimulated C-peptide, insulin use, hypoglycemic events and immunological responses.

At 104 weeks, or 60 weeks after the last dose of alefacept, both the 4-h and the 2-h C-peptide AUCs were signifi-

*Corresponding author: Yasuko Uchigata

Tel: +81-3-3353-8111 ext. 27110

Fax: +81-3-3358-1941 Direct: +81-3-5269-7439

E-mail address: uchigata.dmc@twmu.ac.jp

Received 5 February 2016; revised 10 February

2016; accepted 12 February 2016

cantly greater in the alefacept group than in the placebo group ($P = 0.002$ and $P = 0.015$, respectively). Exogenous insulin requirements were kept lower ($P = 0.002$), and rates of major hypoglycemic events were reduced by approximately 50% ($P < 0.001$) in the alefacept group compared with the placebo group at 24 months. There was no apparent between-group difference in glycemic control or adverse events. Alefacept treatment depleted CD4+ and CD8+ central memory T cells (Tcm) and effector memory T cells (Tem; $P < 0.01$), preserved regulatory T cells, increased the ratios of Treg to Tem and Tcm ($P < 0.01$), and increased the percentage of PD-1+CD4+ Tem and Tcm ($P < 0.01$). The investigators concluded that in patients with newly diagnosed type 1 diabetes, two 12-week courses of alefacept preserved C-peptide secretion, reduced insulin use and hypoglycemic events, and induced favorable immunological profiles at 24 months, well over 1 year after cessation of the therapy.

C-peptide AUCs were significantly greater in the alefacept group than in the placebo group, and exogenous insulin requirements were lower in the alefacept group than in the placebo group at 104 weeks without an apparent difference in glycated hemoglobin level, and it should be noted that the differences became smaller at 104 weeks compared with 52 weeks (Figure 1).⁵ Here, we examine the enrolment criteria of the participants. Eligible participants had to be aged 12–35 years at the time of screening, fewer than 100 days from diagnosis at the time of enrolment, positive for at least one diabetes-associated autoantibody (insulin antibody [if duration of insulin therapy was fewer than 10 days], GAD-25 antibody, IA-2 antibody, ZnT8 antibody or ICA) and have a peak stimulated C-peptide of more than 0.2 nmol/L during a mixed meal tolerance test. Mean insulin use (units per kg per day) of alefacept and placebo groups were 0.33 and 0.29 units, respectively (not significant). An important caution was participants who had partial β -cell function at the screening.

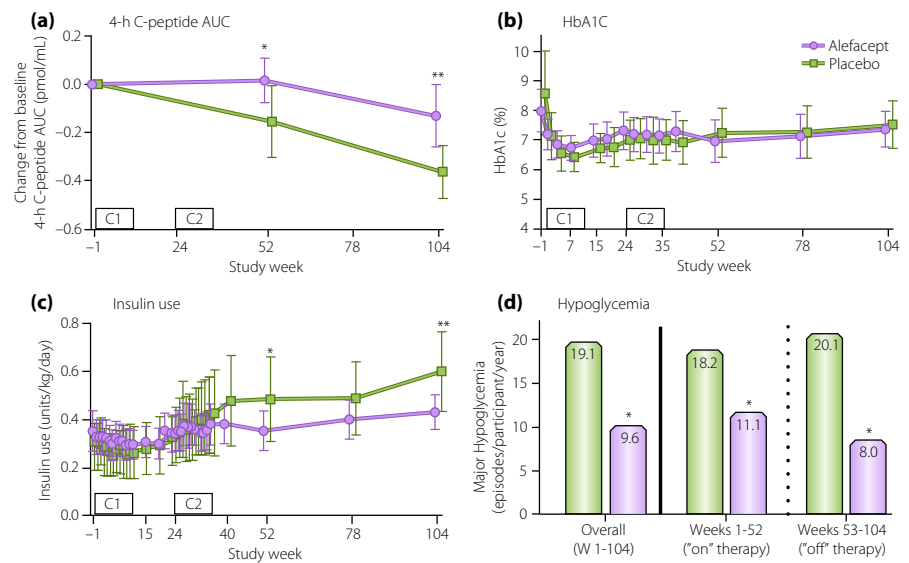


Figure 1 | Clinical responses from baseline to 24 months in participants assigned to alefacept and placebo in the intention to treat (ITT) sample. (a) Change in 4-h C-peptide AUC. $*P = 0.019$, $**P = 0.002$. (b) Change in HbA1c. (c) Change in exogenous insulin requirements. $*P = 0.020$, $**P = 0.002$. Data were analyzed by fitting ANCOVA models with adjustment for baseline levels and plotted as unadjusted means \pm 95% CI. P values are two-sided. (d) Rate of major hypoglycemic events. Event rates between the two groups were compared using Poisson regression. $*P < 0.001$. For all analyses, the number of evaluable subjects (n) at each time point is shown in this figure. C1 and C2 denotes the two 12-week treatment courses. For additional details, see https://www.itntrials.org/T1DAL_fig2.url. AUC, area under the curve; HbA1c, glycated hemoglobin. Reproduced with permission by American Society for Clinical Investigation, *J Clin Invest*, 2015⁵. Copyright and all rights reserved.

At 104 weeks, the alefacept group was divided into complete responders (26%), partial responders (49%) and worse responders (26%), whereas three responders of the placebo group at 104 weeks were 8, 25 and 67%, respectively. The alefacept group had a greater percentage of complete responders, and a lower percentage of worse responders. Glycated hemoglobin levels were maintained at approximately 7% in both groups (Figure 1b). If both groups used more exogenous insulin, they would preserve β -cell destruction more than what was found in the present study. How about another dose of alefacept for the alefacept group?

The investigators showed that the relationship between changes in peripheral blood T cell subsets and the clinical response remains unclear. In the alefacept group, complete responders (C-peptide AUC values at 2 years equal to or greater than baseline values) did not differ in terms of frequencies of Tcm,

Tem or Tregs in the periphery when compared with all participants who did not meet the complete response criterion or when compared only with participants with the worst response. They mentioned that this finding is consistent with the experience in psoriasis, where treatment with alefacept resulted in a clinical response rate of 40–60%, but response was poorly correlated with changes in the number of memory CD4+ T cells in the peripheral circulation. However, an alefacept clinical trial to arrest kidney transplant rejection was stopped by the company at the phase 2 stage because of no significant outcome in 2011.

The investigators also observed an increase in the percentage of CD4+ Tem and Tcm expressing PD-1 during and after treatment. Targeted expression of the PD-1 ligand, PD-L1, was reported to lead to decreased proliferation and increased apoptosis of infiltrating CD4+ T cells with

robust reversal of hyperglycemia; however, overexpression of PD-1 in general might lead to an immune suppressive state.

Another dose of alefacept to the alefacept group might be a possibility to prevent β -cell destruction under sufficient surveillance of malignancy and infections.

ACKNOWLEDGMENTS

YU has received unrestricted research expenses from Alcon, Arkray, Astellas, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Johnson & Johnson, Kaken, KCI, Kissei, Kowa, Kyowa Hakko Kirin, Mitsubishi Tanabe, Mochida, MSD, Nipro, Novartis, Novo Nordisk, Ono, Otsuka, Pfizer, Roche, Sanofi, Santen, Sumitomo Dainippon, Takeda, Teijin, Terumo and Torii.

DISCLOSURE

The author declares no conflict of interest.

Yasuko Uchigata*

*Diabetes Center, Department of
Medicine III, Tokyo Women's Medical
University School of Medicine, Tokyo,
Japan*

REFERENCES

1. Buestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature* 2010; 464: 1293–1300.
2. von Herrath M, Peakman M, Roep B. Progress in immune-based therapies for type 1 diabetes. *Clin Exp Immunol* 2013; 172: 186–202.
3. Haider AS, Lowes MA, Gardner H, *et al.* Novel insight into the agonistic mechanism of alefacept in vivo: differentially expressed genes may serve as biomarkers of response in psoriasis patients. *J Immunol* 2007; 178: 7442–7449.
4. Rigby MR, DiMeglio LA, Rendell MS, *et al.* Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL study): 12 month results of a randomized, double-blind, placebo-controlled phase 2 trial. *Lancet Diabetes Endocrinol* 2013; 1: 284–293.
5. Rigby MR, Harris KM, Pinckney A, *et al.* Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. *J Clin Invest* 2015; 125: 3285–3296.

Doi: 10.1111/jdi.12501