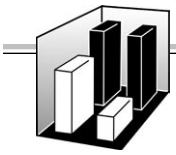
CLINICAL TRIALS REPORT



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Progress, But Not Yet Ready for Clinical Use: Interrupting Immune-mediated Destruction of Pancreatic β Cells in Type 1 Diabetes

Keymeulen B, Vandemeulebroucke E, Ziegler AG, et al.: **Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes.** *N Engl J Med* 2005, **352:**2598–1608.

Rating: •Of importance.

Introduction: Immune-mediated destruction of β cells underlies the development of type 1 diabetes. Despite the poor clinical picture for individuals with type 1 diabetes, lifelong treatment with immunosuppressive therapy has been considered an inappropriate therapeutic tradeoff. As a result, the aim has been to develop therapies to induce "immune tolerance," a short-term treatment that would result in long-term amelioration of the immune attack. Studies in the nonobese diabetic mouse suggested that short-term treatment with monoclonal antibodies against CD3 could result in long-term remission of disease. Two humanized anti-cd3 antibodies have been developed for clinical use. One, hOKT3γ1(ala-ala), was used in an open-labeled pilot trial in subjects with recently diagnosed diabetes; it suggested that treated subjects had better β-cell function than control subjects at 1 year after treatment [1]. The other, ChAglyCD3, was used in this phase 2, placebo-controlled trial.

Aims: To determine whether ChAglyCD3 treatment of individuals with recently diagnosed type 1 diabetes would result in preservation of β-cell function at 6 months.

Methods: This was a multicenter, placebo-controlled, randomized trial for islet antibody-positive subjects between ages 12 and 39, who were treated with insulin for less than 4 weeks, and had a random C-peptide level of greater than 0.2 nmol/L. Forty subjects were in each group, with a median age of approximately 27 years.

The primary outcome was determined from a 3-hour euglycemic period maintained by intravenous insulin infusion, followed by an infusion of glucose to reach levels of 180 to 250 mg/dL. At 140 minutes, 1 mg of intravenous glucagon was administered. The area under the curve (AUC) for glucose and glucagon-induced C-peptide release was calculated. The first nine patients received a dose of 24 mg, followed by infusion of 8 mg/d for 5 days. Due to adverse events after the initial dose, the remaining 71 subjects received six daily infusions of 8 mg or placebo per day.

Results: Results fall into the broad areas of efficacy and safety.

Efficacy:

Primary outcome. The differences between the baseline and 6-month AUC were determined for each group for both glucose-stimulated and glucagon-stimulated C-peptide. At month 6, the δ AUC for glucose-stimulated C-peptide in ChAglyCD3-treated subjects was 0.22 nmol/L/min greater than placebo-treated subjects ($P = 0.009$). Similarly, the δ AUC for glucagon-stimulated C-peptide in ChAglyCD3-treated subjects was 0.39 nmol/L/min greater than placebo-treated subjects ($P = 0.006$).

Secondary outcomes. At 6 months, the ChAglyCD3-treated subjects also used less insulin to achieve the same hemoglobin A_{1c} (HbA_{1c}) as the placebo-treated individuals. Similar differences were seen at 12- and 18-month time points.

Post hoc analysis. Dividing the group into those above and below the 50th percentile of baseline C-peptide response suggested that those subjects with higher baseline values had the most benefit from ChAglyCD3 treatment.

Safety:

All ChAglyCD3-treated subjects experienced adverse events during the treatment period, such as fever, headache, gastrointestinal symptoms, arthralgia, myalgias, and rash. Between days 16 to 21, 30 of the treated subjects experienced a syndrome similar to acute mononucleosis with sore throat, fever, and/or cervical adenopathy. Essentially all treated subjects who were studied had laboratory evidence of transient Epstein-Barr virus (EBV) activation. One subject stopped treatment after three 8-mg doses due to catheter sepsis.

Discussion: The authors suggest that short-term treatment with ChAglyCD3 ameliorates the 35% reduction in β-cell function that is seen 18 months after diagnosis. Further, they indicate that the metabolic benefit is most apparent in patients with higher residual β-cell function.

The adverse events that were experienced during treatment were attributed to a transient cytokine release. They emphasized that the EBV activation was transient and that no evidence of post-transplantation lympho-

proliferative disorder or inability to resolve the infection was seen; however, they express caution that long-term follow-up is needed.

Editor's comments

Two different "non-mitogenic" anti-cd3 antibodies have now been reported to reduce the fall in β-cell function in recently diagnosed patients with type 1 diabetes, thus providing proof of concept. However, many important questions remain before clinical use is recommended.

Efficacy. Most diabetes therapies target HbA_{1c} as an end point because an improvement in HbA_{1c} is accepted by the US Food and Drug Administration as a surrogate for an improved clinical outcome. However, hyperglycemia itself appears to hasten β-cell dysfunction. Thus, interpretation of an intervention trial requires that both groups achieve equal glycemic control, effectively eliminating HbA_{1c} as a potential outcome measure. Although a reduction in insulin dose may signal an improvement in β-cell function, this indirect assessment is confounded by the lifestyle of the patient (and their treating physician). As a result, the Immunology of Diabetes Society [2] and an expert review group convened by the American Diabetes Association [3] concurred that measurement of β-cell function by C-peptide assessments is the most appropriate outcome for intervention trials.

Although there are data that increased C-peptide is associated with less hypoglycemia and less diabetes complications [4,5], it is unknown whether there is a threshold effect, or what duration of persistent β-cell function is needed. Importantly, the Diabetes Control and Complications Trial intensively treated subjects continued to have clinical benefit years after short-term intervention, suggesting that even a transient delay of β-cell destruction may have profound long-term clinical effects. Further, there are many ways to measure β-cell function. Historically, the lack of consistency has made comparisons between studies difficult.

This concern led to the Immunology of Diabetes Society consensus statement that the C-peptide response to a 2-hour mixed-meal tolerance test be included in all intervention trials [2]. Unfortunately, this advice was not followed in the study by Keymeulen et al. This is not to say their chosen assessment of β-cell function is wrong, but rather that this choice makes it difficult to compare between studies. Further, as pointed out by others [6], the data appear to demonstrate the most dramatic difference between groups at 6 months, when the treated group had apparently stable function and the placebo group had a fall in function. Such a fall in β-cell function is not consistently seen in natural history or other control groups of intervention trials. It appears that after the 6-month time point, both groups appeared to have a similar rate of fall until 18 months. If true, these data would suggest that immunologic tolerance was not achieved, but rather that the anti-cd3 treatment had an acute effect transiently improving β-cell function but had no prolonged effect on the underlying destructive process. As noted above, such a short-term effect may prove to be clinically relevant, but it diminishes the enthusiasm for this particular therapy as being unique among immunosuppressants with respect to inducing long-term clinical tolerance. Interestingly, when one examines the post hoc analysis of those who started with higher β-cell function, this pattern is no longer apparent, thus suggesting that a more prolonged effect may occur in a subset of subjects. One can speculate about why this was seen, but too much speculation on post hoc data is dangerous.

Safety. All subjects experienced symptoms attributable to a cytokine release syndrome. The presence of these symptoms with both this drug and hOKT3γ1(ala-ala), however, highlights the fact that although designed to be non-mitogenic, this effort was not completely successful. By itself, if long-term efficacy is able to be demonstrated, such symptoms would not have to limit the clinical use of the drug; however, these symptoms point to the need to pursue a dose-finding study.

More concerning was the almost universal activation of EBV seen in treated subjects. Although subjects appeared to clear this activation, these data highlight the reality that even short-term immunosuppression may carry risk of long-term harm. Surprisingly, there is little information about whether such activation occurs routinely in subjects who receive immunosuppression for other autoimmune diseases. These data emphasize the importance of routine monitoring of EBV viral load in all such clinical trials. Such data will either lead to an understanding that transient activation carries no long-term risk, or will require rethinking of the equation between risk and benefit.

Summary. This report highlights both the promises and the risks of novel therapies to treat the autoimmunity in type 1 diabetes. However, there is not yet clear evidence that anti-cd3 therapies will pose a clinical advantage over other immunosuppressants with more widespread clinical use. Studies testing a combination of mycophenolate mofetil and daclizumab are underway, and studies using rituximab (anti-cd20), thymoglobulin, and combining interleukin-2 and rapamycin are in the final planning stages. Additional strategies to prolong the apparent clinical effect with the anti-cd3 monoclonals are being pursued as well. Other ideas that are being tested include antigen-specific therapies [7–9]. The results of these studies will provide needed information for clinicians.

The goal of stopping β-cell destruction remains worth seeking. Despite marked improvement in diabetes care, the clinical outcome for individuals diagnosed with type

1 diabetes in the 21st century continues to be poor. A new approach is needed, and with these studies such a new approach will surely come.

References

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