B-Lymphocyte Depletion With Rituximab and β-Cell Function: Two-Year Results

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OBJECTIVE

We previously reported that selective depletion of B-lymphocytes with rituximab, an anti-CD20 monoclonal antibody, slowed decline of β-cell function in recent-onset type 1 diabetes mellitus (T1DM) at 1 year. Subjects were followed further to determine whether there was persistence of effect.

RESEARCH DESIGN AND METHODS

Eighty-seven subjects (aged 8–40 years) were randomly assigned to, and 81 received, infusions of rituximab or placebo on days 1, 8, 15, and 22. The primary outcome—baseline-adjusted mean 2-h area under the curve (AUC) serum C-peptide during a mixed-meal tolerance test (MMTT) at 1 year—showed higher C-peptide AUC with rituximab versus placebo. Subjects were further followed with additional MMTTs every 6 months.

RESULTS

The rate of decline of C-peptide was parallel between groups but shifted by 8.2 months in rituximab-treated subjects. Over 30 months, AUC, insulin dose, and HbA_{1c} were similar for rituximab and placebo. However, in evaluating change in C-peptide over the entire follow-up period, the rituximab group means were significantly larger as compared within assessment times with the placebo group means using a global test ($P = 0.03$). Odds ratio for loss of C-peptide to <0.2 nmol/L following rituximab was 0.565 ($P = 0.064$). B-lymphocytes recovered to baseline values by 18 months. Serum IgG levels were maintained in the normal range but IgM levels were depressed.

CONCLUSIONS

Like several other immunotherapeutic approaches tested, in recent-onset T1DM, rituximab delays the fall in C-peptide but does not appear to fundamentally alter the underlying pathophysiology of the disease.

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At the time of diagnosis, most patients with autoimmune-mediated type 1 diabetes mellitus (T1DM) retain some β-cell function as measured by C-peptide responses. Long-term retention of residual β-cell function is associated with a reduction of severe hypoglycemic episodes and complications (1,2). Thus an

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**The TrialNet Anti-CD20 Study Group is listed in the Supplementary Data online.*

intervention that achieves persistent improvement of endogenous insulin production would be expected to improve management and reduce long-term complications.

The immunopathogenesis of β-cell destruction is typically associated with T-lymphocyte autoimmunity. Thus several clinical trials to prevent or treat T1DM have targeted T-lymphocytes (3,4) or their activation (5). B-lymphocyte–directed therapies have been shown to prevent and even reverse T1DM in the nonobese diabetic mouse model (6). In human beings, B-lymphocytes can be selectively depleted using the anti-CD20 monoclonal antibody, rituximab (7). We previously reported that such selective depletion of B-lymphocytes resulted in significant preservation of insulin secretion for 1 year (8). We now report the safety and efficacy of this treatment with further follow-up.

RESEARCH DESIGN AND METHODS

Study Design and Procedures

This phase 2 clinical trial was registered with ClinicalTrials.gov (NCT00279305). The complete study design and results of the 1-year end points have been previously reported (8). Briefly, at 12 sites in the U.S. and Canada, a total of 87 patients were enrolled in a double-masked parallel group design and were randomized in a 2:1 ratio, with 57 subjects receiving rituximab and 30 subjects receiving placebo. The major time focus for the current report was 24 months, although longer-term data for some subjects is included. While subjects were given the overall results of the study after year 1, participants and staff remained masked to individual study assignment and data until all subjects had completed at least 2 years of follow-up and data lock had occurred. Data reported here were obtained prior to unmasking of the clinical site and study participant as to treatment assignment.

Each subject received one course of four intravenous infusions of rituximab (each infusion being 375 mg/m^2) or placebo on study days 1, 8, 15, and 22. No additional courses or treatments with rituximab or other immunosuppressive or immunomodulatory drugs were allowed or given during the follow-up period. Acetaminophen and diphenhydramine were administered as premedication before each infusion to attenuate infusion-related events.

Predefined secondary outcomes at 24 months included 2-h area under the curve (AUC) serum C-peptide during a mixed-meal tolerance test (MMTT), changes in HbA_{1c} and insulin dose at 6 month intervals, time to first stimulated peak C-peptide of less than 0.2 nmol/L, and safety. Safety outcomes focused on infections and laboratory assessments, particularly white blood cell counts and immunoglobulin levels.

The study protocol is available at the Type 1 Diabetes TrialNet public website www.diabetestrialnet.org.

Statistical Analyses

Details of the statistical plan are included in our earlier report (8). The intention-to-treat principle was prespecified to be applied to all subjects with known end points; there were 78 analyzable subjects at 2 years (8).

The *P* values associated with the intention-to-treat comparisons of the primary and secondary end points are one-sided to be consistent with the design of the trial (although the earlier publication (8) reported two-sided *P* values in accordance with the journal's rules). The prespecified analysis method for C-peptide mean AUC, HbA_{1c}, and total daily insulin dose was an ANCOVA model adjusting for baseline age, sex, baseline value of the dependent variable, and treatment assignment. The significance levels associated with the treatment effect are from the Wald test (from the fitted model) and are one-sided in agreement with the statistical design. A normalizing transformation of $\log(X_{C-Pep}+1)$ was prespecified for C-peptide AUC mean, and normal plots of the residuals indicated that it was adequate. The C-peptide mean AUC equals the AUC divided by the 2-h interval (i.e., AUC/120). The AUC was computed using the trapezoidal rule from the timed measurements of C-peptide during the MMTT. The 95% CIs of the predicted group means were calculated from the linear model. The CI for percentage change was derived by using a bootstrap procedure.

The time to first stimulated peak C-peptide of less than 0.2 nmol/L was analyzed using standard survival methods (Cox model and Kaplan–Meier method). Adverse events were analyzed using contingency table methods, and the significance levels are from the Pearson χ^2 test (two-sided). Mean rate of change of C-peptide AUC mean from 6 to 30 months (3-month assessment was not included to maintain a uniform contribution of scheduled assessments over time) was estimated using a mixed effects model with both random intercept and slope adjusting for age, sex, baseline C-peptide AUC mean, and treatment assignment. The initial fit included a fixed interaction effect of treatment and time but was removed because of the lack of any statistical evidence of it being other than zero. To assess the treatment effect over the entire time period, a similar mixed model was fitted to the data, except time was defined without structure and grouped by 6-month intervals (6–30 months).

Missing values became a significant issue at the 30-month follow-up assessment, thus potentially diminishing the randomized treatment group comparison. For this reason, no significance tests at 30 months are reported, but point estimates and the corresponding 95% CIs are provided in the graphs.

RESULTS

The baseline characteristics of the two groups were previously reported (8). Supplementary Fig. 1 depicts the patient flow diagram, showing enrollment/randomization and retention of subjects during the study through 24 months of follow-up. In the rituximab group, 49/49 subjects reaching the 12-month follow-up point had a follow-up at 24 months, compared with 28/29 in the placebo group.

Effectiveness

Fig. 1*A* displays the results of the linear modeling of mean AUC of C-peptide over 2 h (nmol/L) adjusted for sex, age, and baseline C-peptide. As reported previously, the study-defined primary end point of AUC mean at 1 year was significantly better for the rituximab group: 0.56 (95% CI 0.50–0.63) and 0.47

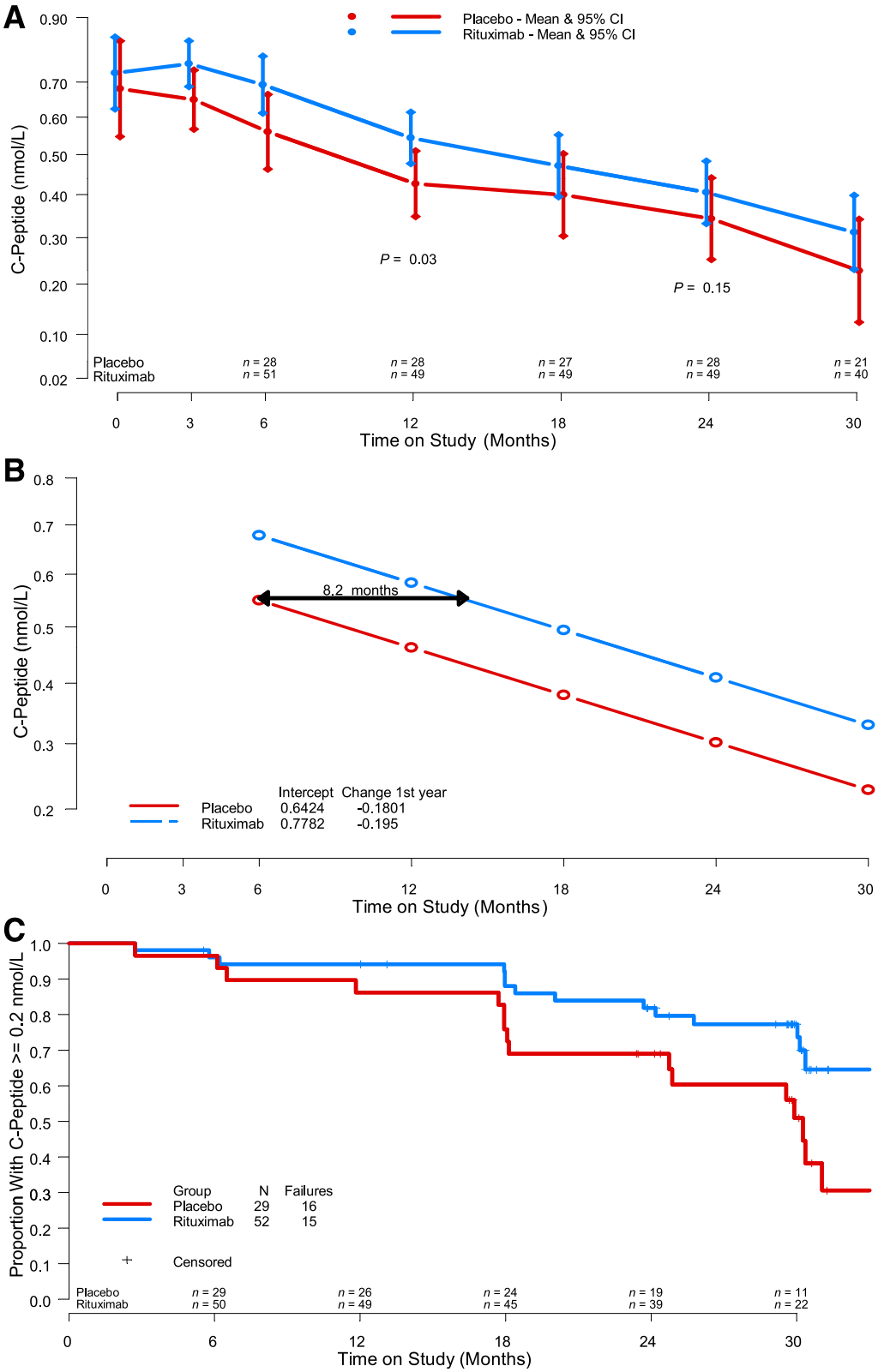

Figure 1—*A*: Linear modeling of mean AUC of C-peptide over 2 h, over time by treatment group. Number of subjects available for analysis is displayed along the *x* axis. *B*: Rate of fall (slope) in C-peptide AUC. The placebo-predicted line leads the rituximab line by 8.2 months. The model assumed that each subject's C-peptide values on the $\log(X_{C-Pep}+1)$ scale tended to follow a straight line (i.e., two random effects: the intercept and constant decay rate over time). *C*: Time to C-peptide failure by treatment group. C-peptide failure was defined as the first time at which the maximum C-peptide during a 2-h MMTT was <0.2 nmol/L.

(95% CI 0.39–0.55) nmol/L for the rituximab and placebo groups, respectively (percentage difference 20%; *P* = 0.03; two-sided) (8). However, at the later time points, while the mean AUC in the rituximab group was still greater, the Wald test was no longer significant. The mean AUC at 2 years was 0.398 (95% CI 0.326–0.473) and 0.336 (95% CI 0.245–0.433) nmol/L for the rituximab and placebo groups, respectively (*P* = 0.15). The percentage difference in means was 18% higher in the rituximab group (95% CI −22.3 to 63.8). A ladder plot of subgroup analyses for AUC of C-peptide is included as Supplementary Fig. 2.

A longitudinal analysis was conducted in an attempt to quantify the change in C-peptide over the entire follow-up period. Four-hundred fifty observations were used in fitting the linear mixed model. When no mathematical relationship was specified across time, the rituximab group means were significantly larger as compared within assessment times with the placebo group means using a global test (*P* = 0.03); the trend is that the differences become smaller with each successive follow-up assessment (6 to 30 months: 0.116, 0.106, 0.102, 0.0970, 0.0903). When a linear relationship was specified across time, both for subject and population means, the associated Wald test for treatment effect was significant (*P* = 0.014) (Fig. 1*B*). When evaluating the difference in decay rates by treatment group, the test was not significant (*P* = 0.45; two-sided). When specifying parallel lines for the population means in the model, the rituximab mean line followed after the placebo line by 8.2 months (95% CI 0.827–15.6).

The C-peptide level was used to define another secondary end point called time to C-peptide failure: the first point in time after initiating dosing with study medication when the maximum of the timed C-peptide assessments during a 2-h MMTT was below 0.2 nmol/L (Fig. 1*C*). Using the Cox model for treatment group and adjusting for baseline C-peptide, sex, and age, the *P* value is 0.064. The relative risk estimate of failure in the rituximab group from the model was 0.565 (95% CI 0.271–1.177).

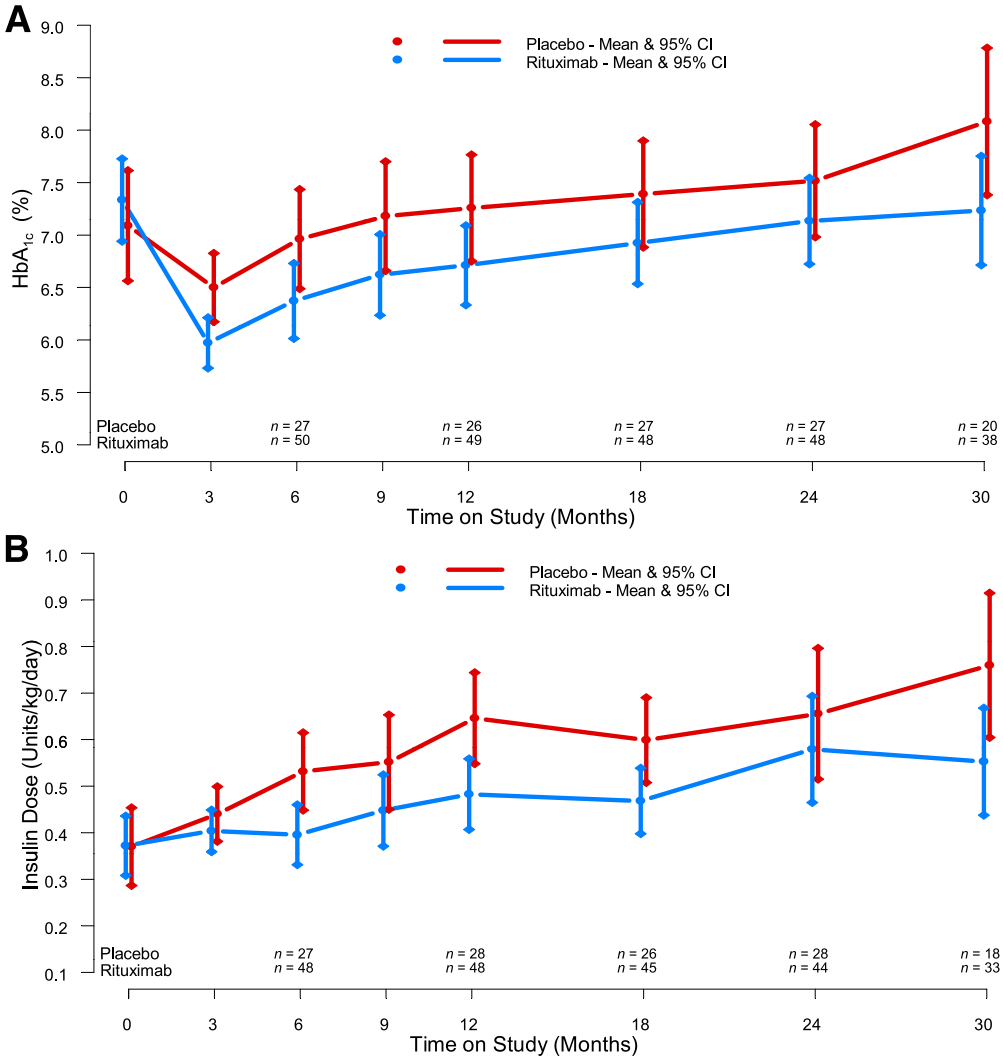

Figure 2—*A*: HbA_{1c} and 95% confidence limits over time by treatment group. *B*: Insulin dose (units per kilogram) over time by treatment group. Number of subjects available for analysis is displayed along the *x* axis.

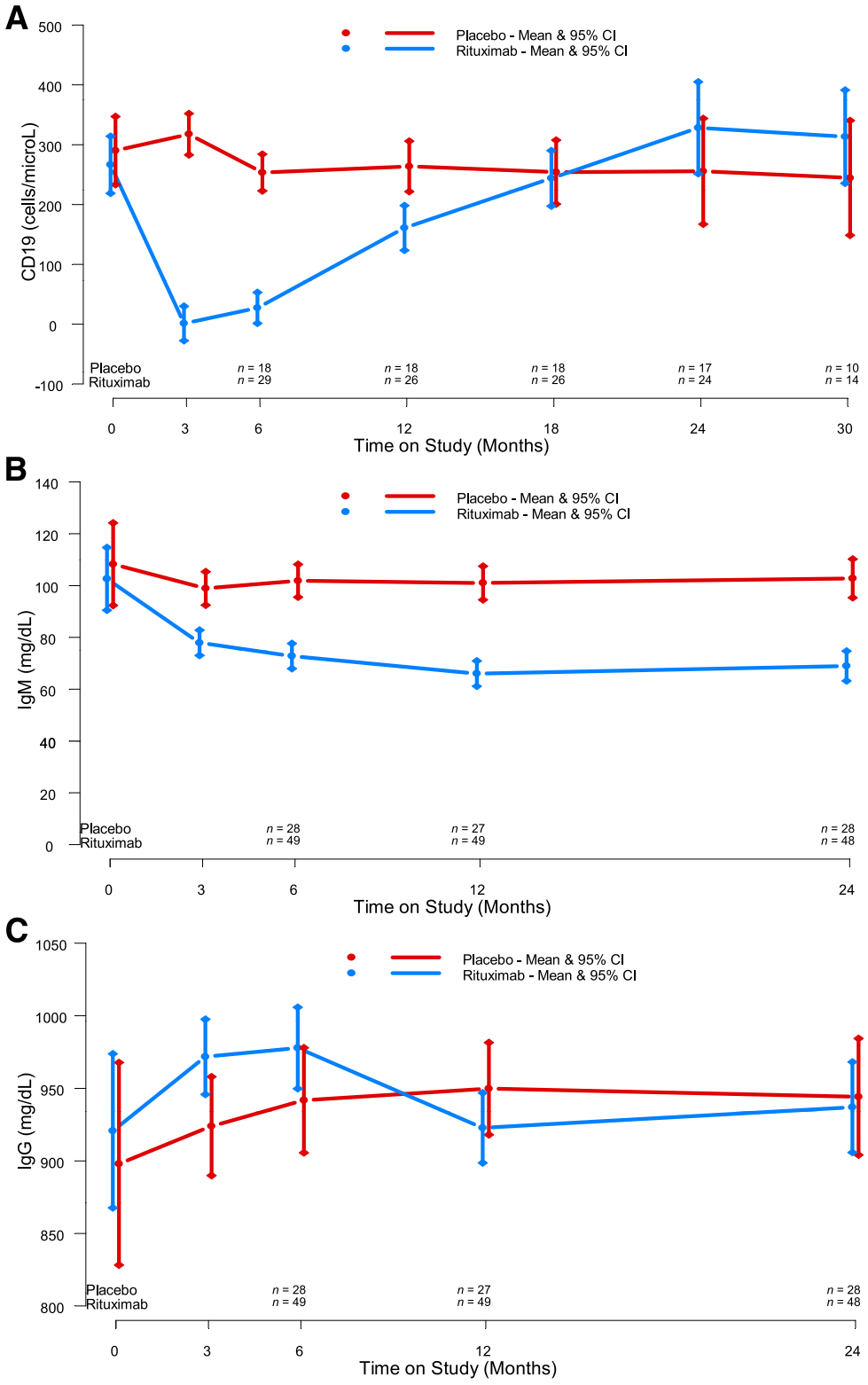

Figure 3—*A*: Absolute CD19 counts over time by treatment group. Multiparameter flow cytometry was performed by the Immune Tolerance Network (at Roswell Park Cancer Institute, Buffalo, NY) from fresh blood. *B*: IgM (milligrams/deciliter and 95% CI) concentrations over time by treatment group. *C*: IgG (milligrams/deciliter and 95% CI) concentrations over time by treatment group. Number of subjects available for analysis is displayed along the x-axis.

As previously reported (8), the rituximab group had lower HbA_{1c} (Fig. 2*A*) (6.76 ± 1.24 versus 7.00 ± 1.30% at 12 months; $P \leq 0.0001$) and insulin dose (Fig. 2*B*) (0.39 ± 0.22 versus 0.48 ± 0.23 units/kg at 12 months; $P \leq 0.0001$). Both values were lower in the rituximab group at 18 and 24 months but were no longer significantly different from the placebo group.

B-Lymphocyte Depletion

CD19 cells were depleted by rituximab ($P \leq 0.0001$) and gradually returned to baseline values by 18 months and remained similar to the control group at 24 months; they were relatively stable in the placebo group (Fig. 3*A*). After analysis of the 1-year data, it was decided to stop performing flow cytometry beyond 2 years of follow-up. Thus the numbers of such measurements at 30 months are fewer but are consistent with the 24-month data, indicating no long-term B-lymphocyte depletion.

Safety

During long-term follow-up, as compared with the first year, there were substantially fewer adverse events (Supplementary Table 2), with fewer subject reports in both groups; most were mild, grade 1 and 2, with none being grade 4. Infections were slightly more common in the rituximab group, but this difference was not significant. These included grade 1 and 2 conjunctivitis ($n = 2$), Strep throat ($n = 2$), upper respiratory infection ($n = 1$), and a finger infection ($n = 1$).

IgM levels fell from baseline in the rituximab group, an effect that persisted at 24 months ($P < 0.0001$) (Fig. 3*B*). The IgG concentrations did not differ significantly between the two groups and remained similar to that at baseline (Fig. 3*C*). No subject required treatment for hypogammaglobulinemia. There were no adverse effects on routine laboratory parameters.

CONCLUSIONS

As noted in the INTRODUCTION, B-lymphocyte–directed therapies have shown beneficial effects in the nonobese diabetic mouse (6). In autoimmune diseases, B-lymphocytes are thought to play a pathogenic role as antigen-presenting cells and may provide help in the activation of T-lymphocytes that are the mediators of autoimmune destruction (6). Therefore, we conducted a trial with rituximab, an anti-CD20 monoclonal antibody that targets B-lymphocytes (8). We have previously reported that a single 4-week course of rituximab within 3 months of the time of diagnosis significantly preserves β-cell function and is associated with a lower HbA_{1c} and lower insulin dose at 1 year (8). In following these subjects up to 30 months after randomization, the rate of fall in the C-peptide AUC paralleled the fall seen in the control group, suggesting that rituximab did not fundamentally alter the underlying pathophysiology of disease. However, the early rituximab treatment did delay this fall in C-peptide, as compared with the control group, by 8.2 months, resulting in an overall greater preservation of β-cell function when all time points were considered (Fig. 1*B*). Although C-peptide AUC, HbA_{1c}, and insulin dose per kilogram tended to be more favorable in the rituximab group than the placebo group in follow-up, there is waning of the effect of rituximab as demonstrated by the lack of statistical difference in these parameters at the 2-year time point. The parallel fall in AUC may reflect resumption of ongoing immune-mediated destruction of β-cells, although without a true marker of the autoimmune response, this remains conjecture. Whether repeat dosing with anti-CD20 or other agents could achieve a more prolonged response without increasing adverse events is not known. It is interesting to note that in the other recent studies that showed beneficial effect of immune intervention in T1DM (3–5), longer-term follow-up also revealed a decline in effect over time (9–11). Although qualitatively similar, direct comparison with the results in the current study is difficult.

When the study was designed, it was assumed that future rituximab dosing might be needed for optimal effect. However, without proof that the treatment was effective and no previous data on the safety of B-lymphocyte depletion in this population, only a single course of therapy was provided. In the initial report, other than the cytokine-associated reaction mostly to the first dose of rituximab, there were no other unusual safety events and particularly no increased rates of infection. This current paper updates that safety analysis. The therapy continued to be safe during longer follow-up. As seen with previous rituximab trials, the B-lymphocyte counts returned to baseline levels after approximately 18 months. The reduction of IgM levels reported at 1 year persisted at 2 years. Reduction of IgM levels has been consistently seen across rituximab studies (12,13), but the mechanism and clinical implications are unclear. In contrast, IgG levels remained stable over the entire period. We have reported that antibody responses to neoantigens and to recall immunization, which were decreased during the time of depletion of B-lymphocytes, returned toward normal as B-lymphocyte counts recovered (14).

In summary, a single course of four infusions of rituximab over 1 month shortly after the diagnosis of T1DM appears to delay the fall in C-peptide by 8.2 months with minimal safety concerns. This trial now paves the way for other approaches targeting B-lymphocytes in the treatment of T1DM, such as extended or repeat dosing with rituximab, use of alternative anti-CD20 (15,16) or other anti-B-lymphocyte antibodies [e.g., anti-CD19 (17)] or therapies that block the BAFF pathway (18). We continue to caution against the use of rituximab for treatment of new-onset T1DM outside carefully monitored and controlled clinical trials.

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Duality of Interest. Genentech (San Francisco, CA) and Biogen Idec (Cambridge, MA) provided rituximab (Rituxan) and the matching placebo but had no involvement with the design, conduct, or management of the study; the collection, analysis, or interpretation of the data; or the preparation of the manuscript. There are no agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines. Roche Diagnostics provided blood glucose monitoring meters and strips to research subjects. M.D.P. reported serving on advisory boards for Genentech/Roche, Johnson and Johnson, and Eli Lilly. C.J.G. reports receiving grants from Bayhill Therapeutics, Diamyd, and Tolerx. D.J.B. reports receiving a grant from Diamyd. S.E.G. reports serving on an advisory board for Genentech. R.G. reports receiving grants from Diamyd and Tolerx. P.A.G. reports serving on advisory boards for Genentech, Eli Lilly, Sanofi, and Tolerx and receiving grants from Bayhill Therapeutics, Diamyd, Macrogenics, Omni BioTherapeutics, and Tolerx. J.B.M. reports serving on an advisory board for Amgen. A.M. reports serving on an advisory board for Pfizer and receiving grants from Tolerx, Merck, and Osiris Therapeutics. P.R. reports serving on advisory boards for Amgen, AstraZeneca, MannKind, and Novo Nordisk; serving on speakers bureaus for Merck and Novo Nordisk; and receiving grants from Aegera, Andromeda Biotech, Bayhill Therapeutics, Biodel, Boehringer Ingelheim, Calibra, CPEX, Generex, Hoffmann-La Roche, MannKind, Novo Nordisk, Osiris Therapeutics, and Reata. H.R. reports serving on advisory boards for Genentech/Roche, Biogen Idec, and Eli Lilly and receiving lecture fees from Eli Lilly. D.A.S. reports serving on advisory boards for Eli Lilly and GlaxoSmithKline and receiving a grant from Diamyd. D.K.W. reports receiving lecture fees from Eli Lilly and Medtronic. D.M.W. reports serving on advisory boards for DexCom and Genentech and receiving grant support from Genentech, Diamyd, and Osiris Therapeutics. J.S.S. reports serving on boards for Amylin Pharmaceuticals, DexCom, Moerae Matrix, Sanofi Diabetes, and Viacyte and receiving grants from Bayhill Therapeutics, Halozyme, Intuity, Mesoblast, and Osiris Therapeutics. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. M.D.P. proposed the trial; conducted the study; researched, collected, and reviewed data; served as study chair; and wrote the first three drafts of the manuscript. Unfortunately, he was killed in a motor vehicle accident before the manuscript could be completed and submitted. C.J.G., B.B., J.P.K., and J.S.S. wrote the manuscript, conducted the study, and collected and reviewed data. D.J.B., S.E.G., R.G., P.A.G., J.B.M., A.M., P.R., H.R., D.A.S., D.K.W., and D.M.W. conducted the study, collected and reviewed data, and reviewed and suggested revisions for the paper. M.D.P., C.J.G., B.B., J.P.K., and J.S.S. made the decision to publish the paper; they are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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