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Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes

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ABSTRACT

BACKGROUND

Type 1 diabetes is an autoimmune disease characterized by progressive loss of pancreatic beta cells. Golimumab is a human monoclonal antibody specific for tumor necrosis factor α that has already been approved for the treatment of several autoimmune conditions in adults and children. Whether golimumab could preserve beta-cell function in youth with newly diagnosed overt (stage 3) type 1 diabetes is unknown.

METHODS

In this phase 2, multicenter, placebo-controlled, double-blind, parallel-group trial, we randomly assigned, in a 2:1 ratio, children and young adults (age range, 6 to 21 years) with newly diagnosed overt type 1 diabetes to receive subcutaneous golimumab or placebo for 52 weeks. The primary end point was endogenous insulin production, as assessed according to the area under the concentration–time curve for C-peptide level in response to a 4-hour mixed-meal tolerance test (4-hour C-peptide AUC) at week 52. Secondary and additional end points included insulin use, the glycated hemoglobin level, the number of hypoglycemic events, the ratio of fasting proinsulin to C-peptide over time, and response profile.

RESULTS

A total of 84 participants underwent randomization — 56 were assigned to the golimumab group and 28 to the placebo group. The mean (±SD) 4-hour C-peptide AUC at week 52 differed significantly between the golimumab group and the placebo group (0.64±0.42 pmol per milliliter vs. 0.43±0.39 pmol per milliliter, P<0.001). A treat-to-target approach led to good glycemic control in both groups, and there was no significant difference between the groups in glycated hemoglobin level. Insulin use was lower with golimumab than with placebo. A partial-remission response (defined as an insulin dose–adjusted glycated hemoglobin level score [calculated as the glycated hemoglobin level plus 4 times the insulin dose] of ≤9) was observed in 43% of participants in the golimumab group and in 7% of those in the placebo group (difference, 36 percentage points; 95% CI, 22 to 55). The mean number of hypoglycemic events did not differ between the trial groups. Hypoglycemic events that were recorded as adverse events at the discretion of investigators were reported in 13 participants (23%) in the golimumab group and in 2 (7%) of those in the placebo group. Antibodies to golimumab were detected in 30 participants who received the drug; 29 had antibody titers lower than 1:1000, of whom 12 had positive results for neutralizing antibodies.

CONCLUSIONS

Among children and young adults with newly diagnosed overt type 1 diabetes, golimumab resulted in better endogenous insulin production and less exogenous insulin use than placebo. (Funded by Janssen Research and Development; T1GER ClinicalTrials.gov number, NCT02846545.)

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*A complete list of the investigators in the T1GER Study is provided in the Supplementary Appendix, available at NEJM.org.

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Type 1 diabetes is an autoimmune disease characterized by progressive loss of pancreatic beta cells that leads to lifelong dependence on insulin therapy.[1] More than 13 million people are affected by type 1 diabetes, and the incidence increases by 3 to 4% per year globally.[2-4] Even with important technological and pharmaceutical advances, the achievement of metabolic control in patients with type 1 diabetes remains challenging and limited.[5] A treatment that prevents or delays beta-cell loss would be of great benefit.[6]

In 2015, a staging taxonomy was developed to characterize phases of type 1 diabetes.[7] Stages 1 and 2 are presymptomatic phases that are characterized by the development of autoimmunity and dysglycemia, respectively; stage 3 is defined as overt disease requiring exogenous insulin therapy. Most efforts to prevent or slow disease progression have been directed at patients with stage 3 disease.[8-10] Despite decades of research, a limited number of immune-modulating drugs have been shown to slow disease progression, and no drug has been approved as a disease-modifying therapy for type 1 diabetes.[11-15]

Tumor necrosis factor α (TNF-α) is a proinflammatory cytokine that appears to play a role in the development and progression of several autoimmune diseases.[16,17] It is directly toxic to pancreatic beta cells. In nonobese diabetic murine models of type 1 diabetes, TNF-α has been shown to promote the development of autoimmune diabetes, whereas TNF-α blockers protect the mice from such development, depending on the treatment approach and age of the mice.[18-22] Patients with new-onset overt type 1 diabetes generally have elevated serum TNF-α levels.[23]

Golimumab is a human IgG1-κ monoclonal antibody specific for human TNF-α and is approved for the treatment of several autoimmune diseases, such as rheumatoid arthritis and ulcerative colitis, in adults in the United States, Europe, and other regions.[24] Golimumab is approved for the treatment of polyarticular juvenile idiopathic arthritis and nonradiographic axial spondyloarthritis in children 2 years of age or older in Europe and other regions.[25] Here, we investigated whether treatment with golimumab would preserve beta-cell function and improve diabetes-related clinical and metabolic measures in children and young adults with newly diagnosed overt (stage 3) type 1 diabetes.

Methods

Trial Design and Oversight

We conducted this phase 2, multicenter, randomized, placebo-controlled, double-blind, parallel-group trial at 27 sites in the United States. The trial included a screening period of up to 4 weeks, a 52-week treatment period (data reported here), and a 52-week off-therapy follow-up period, which is currently in progress. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. Ethical approval was obtained at each trial site, and written informed consent was obtained from each participant or from the participant's caregiver with the participant's assent. The trial was sponsored by Janssen Research and Development.

The trial was designed by nine of the authors. All the authors collected and analyzed the data, wrote the first draft of the manuscript, contributed to revisions, participated in the decision to submit the manuscript for publication, and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. Professional medical writers (funded by the sponsor) contributed to the preparation of an earlier version of the manuscript. The sponsor participated in the design of the trial, in writing the manuscript, and in the decision to submit the manuscript for publication.

Participants and Randomization

The participants were between 6 and 21 years of age, had received a diagnosis of type 1 diabetes according to American Diabetes Association (ADA) criteria, were able to undergo randomization within 100 days after diagnosis, and had a peak C-peptide level of at least 0.2 pmol per milliliter after a 4-hour mixed-meal tolerance test. In addition, all the participants had positive results on testing for at least one of the following antibodies associated with type 1 diabetes: anti–glutamic acid decarboxylase 65, anti–islet antigen 2, anti–zinc transporter 8, anti–islet-cell antigen, or anti-insulin (if the anti-insulin antibody level was obtained within 10 days after the initiation of exogenous insulin therapy).[26] The participants were required to be up to date with and agree to

receive age-appropriate immunizations, except for live vaccines. Patients with a history of other clinically significant diseases, including autoimmune diseases (except stable autoimmune thyroiditis), were excluded.

The participants and trial teams agreed to follow the ADA recommendation, current at the time of the trial, to aim for a target glycated hemoglobin level of less than 7.5% (if <18 years or age) or less than 7.0% (if ≥18 years of age).[1] Total daily insulin use, blood glucose levels, and hypoglycemic events were recorded by the participants at home in an electronic diary.

The participants were randomly assigned in a 2:1 ratio to receive golimumab or placebo. As prespecified in the protocol, randomization was stratified according to the area under the concentration–time curve for C-peptide level in response to a 4-hour mixed-meal tolerance test (4-hour C-peptide AUC) conducted at screening (≤0.66 pmol per milliliter or >0.66 pmol per milliliter).

TREATMENT

On the basis of pharmacokinetic, pharmacodynamic, and safety data, a dosing regimen was developed to rapidly achieve steady-state levels while avoiding substantial TNF-α peak-to-trough fluctuations. Participants with a body weight of less than 45 kg received an induction dose of subcutaneous golimumab of 60 mg per square meter of body-surface area at weeks 0 and 2; participants with a body weight of 45 kg or higher received an induction dose of 100 mg at weeks 0 and 2. The induction doses were followed by maintenance subcutaneous doses of 30 mg per square meter and 50 mg, respectively, at week 4 and every 2 weeks through week 52. After onsite training, injections could be administered by participants or their caregivers using either a 50-mg prefilled syringe (PFS-Ultrasafe) or 45-mg metered injection device (PFS-VarioJect).

END POINTS

The primary end point was endogenous insulin production, as assessed according to the 4-hour C-peptide AUC at week 52. Three secondary end points were the change from baseline in insulin use at week 52, the change from baseline in the glycated hemoglobin level at week 52, and the number of hypoglycemic events through week 52. Hypoglycemia was defined in the protocol as a biochemically confirmed blood glucose level of 70 mg per deciliter (3.9 mmol per liter) or less, irrespective of clinical symptoms and events related to severe hypoglycemia. In addition, hypoglycemic events were categorized as level 1 (blood glucose level, 54 to <70 mg per deciliter [3.0 to <3.9 mmol per liter]), level 2 (blood glucose level, <54 mg per deciliter), or level 3 (a severe event characterized by altered mental or physical status [or both] that requires assistance from another person for recovery).[27] Other prespecified end points were the 4-hour C-peptide AUC, insulin use, the glycated hemoglobin level, and the ratio of fasting proinsulin to C-peptide over time.

In addition to the aforementioned end points, three response profiles at week 52 were prospectively defined — a C-peptide response, defined as either an increase or a minimal decrease (≤5%) from baseline in the 4-hour C-peptide AUC; a partial-remission response, defined as an insulin dose–adjusted glycated hemoglobin level score of 9 or less (calculated as the glycated hemoglobin level [percent] plus 4 times the insulin dose [unit per kilogram of body weight per day])[28]; and a response that met the criteria for both profiles.

Safety end points included adverse events that occurred during the treatment period, serious infections, injection-site reactions, and hypoglycemia. Vital signs and clinical laboratory test results were assessed, and physical examinations were performed.

The C-peptide and proinsulin levels were assessed with the use of two-site immunoenzymometric assays and radioimmunoassay kits (Millipore), respectively, at Northwest Lipid Metabolism and Diabetes Research Laboratory. Serum golimumab concentrations were determined with the use of a validated electrochemiluminescence assay, and the development of antibodies to golimumab was determined by means of a sensitive enzyme immunoassay.[29,30]

STATISTICAL ANALYSIS

The sample-size calculation was based on the number of participants who would need to be enrolled to detect a significant difference between the golimumab group and the placebo group with respect to the primary end point. Owing to skewed C-peptide AUC data, a logarithmic transformation (log[AUC+1]) was performed to normalize

the distribution.[13,14,31,32] A standard deviation of 0.215 was assumed for log(AUC+1), and the back-transformed mean values of the 4-hour C-peptide AUC were assumed to be 0.385 for the placebo group and 0.635 for the golimumab group. We calculated that a sample size of 81 participants and a randomization ratio of 2:1 between the golimumab group and the placebo group would provide the trial 90% power to detect a treatment difference at an alpha level of 0.05 (two-sided) on the basis of a two-sample t-test.

Both efficacy and safety analyses included all the participants who had received at least one dose of golimumab or placebo, which included all the participants who had undergone randomization in this trial. The primary end point was analyzed with the use of a mixed model for repeated measures that was fitted on the log(AUC+1)–transformed C-peptide AUC data. The analysis used the postbaseline log(AUC+1)–transformed C-peptide AUC as the response variable and included categorical effects of sex, treatment, time, and treatment-by-time interaction, as well as continuous covariates of baseline (log[AUC+1]–transformed C-peptide AUC), baseline-by-time interaction, and age. An unstructured covariance matrix was used to model the correlation among repeated measurements within each participant. The secondary end points of the change from baseline in insulin use at week 52 and the change from baseline in the glycated hemoglobin level at week 52 were analyzed with the use of a mixed model for repeated measures. The secondary end point of the number of hypoglycemic events through week 52 was analyzed with the use of a Poisson regression model with a scale variable to determine the treatment effect (the ratio of the rate of hypoglycemic events [the number of events per patient-year of exposure] in the golimumab group to that in the placebo group).

Missing data for all continuous missing outcomes (log[AUC+1]–transformed C-peptide AUC, change from baseline in the glycated hemoglobin level, and change from baseline in insulin use) were assumed to be missing at random and were imputed implicitly with the use of a mixed model for repeated measures. In the analysis of the number of hypoglycemic events, logarithm-transformed exposure to golimumab or placebo through week 52 was included as an offset variable in the model to account for participants who had withdrawn early from the trial. In the analysis of the response profile at week 52 (i.e., C-peptide response, partial-remission response, or C-peptide plus partial-remission response), participants with missing data were included in the same category as those who had not met the response criteria.

Control for multiple comparisons was planned for the analyses of the primary and secondary end points. The primary end point was tested first. The Hochberg approach[33] was applied to test the three secondary end points only if the primary end point was significant at a P value of less than 0.05.

RESULTS

PARTICIPANTS

A total of 108 children and young adults underwent screening, and 84 were randomly assigned to receive either golimumab (56 participants) or placebo (28 participants). Details of the screening, randomization, and follow-up of the participants are provided in Figure S1 in the Supplementary Appendix, available at NEJM.org.

Baseline anthropometric and clinical metabolic characteristics were similar in the trial groups (Table 1). Over 52 weeks, the mean duration of exposure to golimumab and placebo was 47.1 and 49.0 weeks, respectively; during this period, of a possible total of 27 injections, the participants in the golimumab group received a mean of 24.2 injections and those in the placebo group received a mean of 24.9 injections.

PRIMARY END POINT

At baseline, the mean (±SD) 4-hour C-peptide AUC was 0.78±0.40 pmol per milliliter in the golimumab group and 0.88±0.63 pmol per milliliter in the placebo group. At week 52, the 4-hour C-peptide AUC was 0.64±0.42 pmol per milliliter in the golimumab group and 0.43±0.39 pmol per milliliter in the placebo group (P<0.001 after adjustment for the baseline and other prespecified factors detailed above). The mean change from baseline in the 4-hour C-peptide AUC was −0.13 pmol per milliliter (95% confidence interval [CI], −0.23 to −0.03) in the golimumab group and −0.49 pmol per milliliter (95% CI, −0.66 to −0.32) in the placebo group, which represents a

Table 1. Key Characteristics of the Participants at Baseline.*

Characteristic	Golimumab (N=56)	Placebo (N=28)
Age		
Mean — yr	13.9±3.7	14.0±4.0
Distribution — no. (%)		
6 to 11 yr	20 (36)	8 (29)
12 to 17 yr	27 (48)	13 (46)
18 to 21 yr	9 (16)	7 (25)
Male sex — no. (%)	31 (55)	18 (64)
Race — no. (%)†		
White	46 (82)	26 (93)
Black	5 (9)	0
Asian	0	1 (4)
Other	5 (9)	1 (4)
Body weight — kg	55.8±19.8	58.1±23.6
Body-mass index z score	0.49±1.05	0.45±1.06
No. of days from diagnosis of type 1 diabetes to randomization	73.6±19.6	75.5±19.0
No. of days from screening to randomization	22.2±5.1	24.2±4.5
No. of type 1 diabetes–associated antibodies detected at screening — no. (%)‡		
1	1 (2)	0
2	5 (9)	3 (11)
3	13 (23)	8 (29)
4	18 (32)	13 (46)
5	18 (32)	4 (14)
Glycated hemoglobin level — %	7.0±1.1	7.1±1.2
Daily insulin dose — U/kg/day	0.42±0.26	0.44±0.20
4-Hour C-peptide AUC at screening — pmol/ml	0.78±0.40	0.88±0.63

* Plus–minus values are means ±SD. Percentages may not total to 100 because of rounding. 4-Hour C-peptide AUC denotes area under the concentration–time curve for C-peptide level in response to a 4-hour mixed-meal tolerance test.
† Race was reported by the participant or by the participant's parent or guardian. Participants who identified as more that one race or did not report race were classified as other.
‡ The antibodies associated with type 1 diabetes included anti–glutamic acid decarboxylase 65, anti–islet antigen 2, anti–zinc transporter 8, anti–islet-cell antigen, and anti-insulin (if the anti-insulin antibody level was obtained within 10 days after the initiation of exogenous insulin therapy). One participant in the golimumab group who had a documented medical history of autoantibody positivity had missing central-laboratory samples at the time of screening.

mean percent decrease of 12% in the golimumab group and of 56% in the placebo group. A between-group difference in the change from baseline in 4-hour C-peptide AUC over time was observed as early as week 12 (Fig. 1A). The corresponding results for the C-peptide AUC in response to a 2-hour mixed-meal tolerance test and the correlation of the 2-hour with the 4-hour C-peptide AUC results at baseline and at week 52 are consistent with the results of the primary analyses (Figs. S2 and S3).

SECONDARY AND ADDITIONAL END POINTS

Glycemic control, as indicated by the mean (±SD) glycated hemoglobin level, was similar in the golimumab group and the placebo group at baseline (7.0±1.1% vs. 7.1±1.2%) and at week 52 (7.3±1.5% vs. 7.6±1.2%) (Fig. 1B). At week 52,

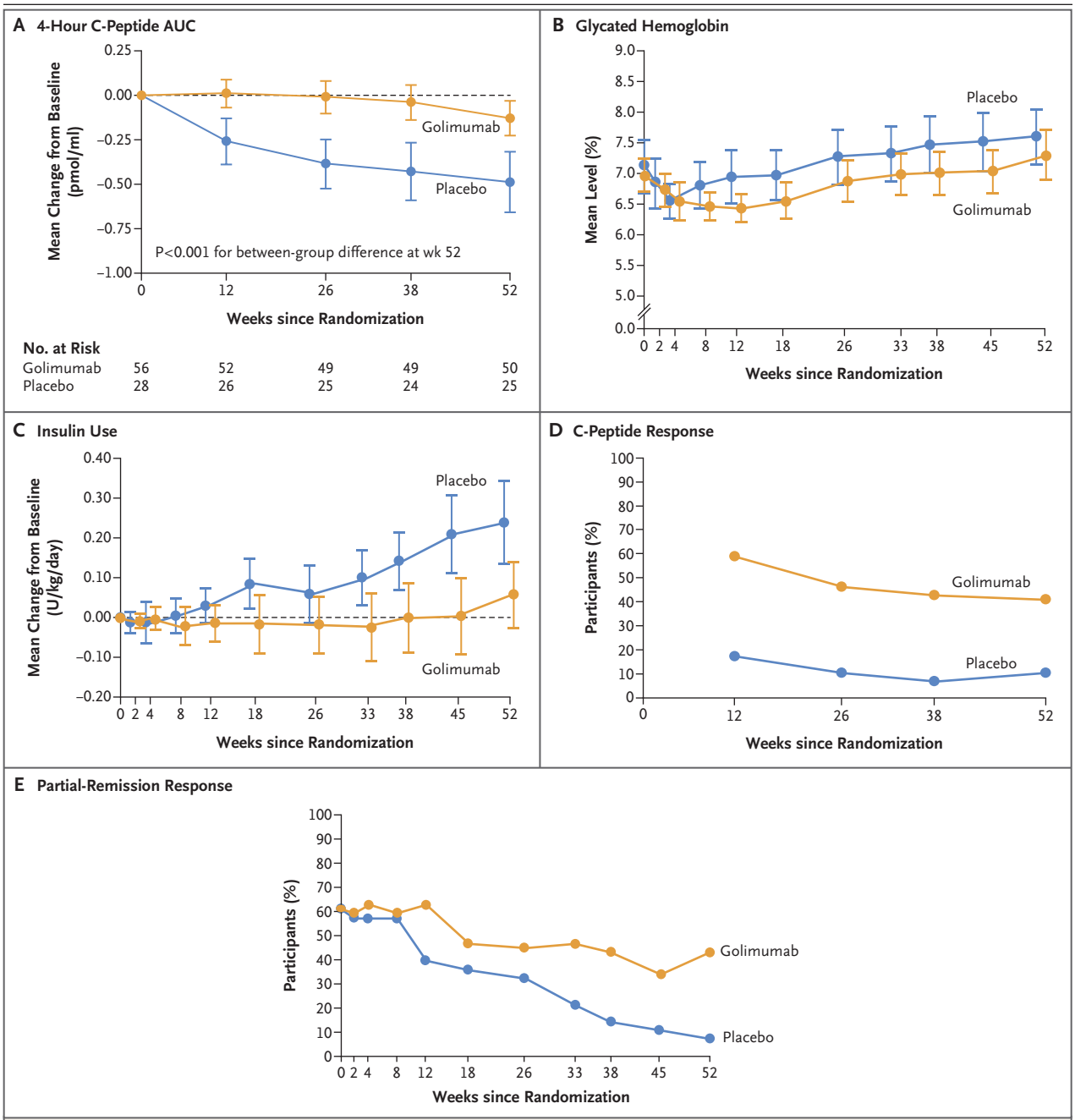

Figure 1. Results for the Primary End Point and Other End Points.

Panel A shows the mean change from baseline through week 52 in the area under the concentration–time curve for C-peptide level in response to a 4-hour mixed-meal tolerance test (4-hour C-peptide AUC, the primary end point), Panel B the mean glycated hemoglobin level through week 52, and Panel C the mean change from baseline through week 52 in daily insulin use. I bars indicate 95% confidence intervals that were estimated with the use of the Wald method; the mean values and 95% confidence intervals were based on observed data. Panel D shows the percentage of participants with a C-peptide response (defined as either an increase or a minimal decrease [≤5%] from baseline in the 4-hour C-peptide AUC), and Panel E the percentage of participants with a partial-remission response (defined as an insulin dose–adjusted glycated hemoglobin level score of ≤9). The between-group difference at week 52 was 30 percentage points (95% confidence interval [CI], 16 to 51) in Panel D and 36 percentage points (95% CI, 22 to 55) in Panel E. The 95% confidence intervals were estimated with the use of Wilson score method.

Table 2. Secondary End Points at Week 52.*

Outcome	Golimumab	Placebo	Treatment Effect (95% CI)†	P Value‡
Glycated hemoglobin level				
All participants — no.	56	28		
Mean glycated hemoglobin level at baseline — %	7.0±1.1	7.1±1.2		
Mean glycated hemoglobin level at wk 52 — %	7.3±1.5	7.6±1.2		
LS mean (±SE) change from baseline at wk 52	0.47±0.21	0.56±0.29	–0.09 (–0.81 to 0.63)	0.80
Insulin use				
All participants — no.	56	28		
Mean dose at baseline — U/kg/day	0.42±0.26	0.44±0.20		
Mean dose at wk 52 — U/kg/day	0.51±0.28	0.69±0.26		
LS mean (±SE) change from baseline to wk 52 — U/kg/day	0.07±0.03	0.24±0.04	–0.18 (–0.27 to –0.08)	0.001
Participants <18 yr of age — no.	47	21		
Mean dose at baseline — U/kg/day	0.42±0.26	0.44±0.20		
Mean dose at wk 52 — U/kg/day	0.51±0.28	0.69±0.26		
LS mean (SE) change from baseline to wk 52 — U/kg/day	0.08±0.03	0.27±0.05	–0.19 (–0.31 to –0.08)	
Participants ≥18 yr of age — no.	9	7		
Mean dose at baseline — U/kg/day	0.31±0.3	0.40±0.19		
Mean dose at wk 52 — U/kg/day	0.37±0.23	0.51±0.33		
LS mean (SE) change from baseline to wk 52 — U/kg/day	0.03±0.04	0.16±0.05	–0.14 (–0.27 to 0.00)	
Hypoglycemic events from baseline through wk 52§				
All participants — no.	56	28		
Mean number of hypoglycemic events§	38.2±35.7	42.9±4.0	0.90 (0.63 to 1.29)	0.80
Level 1	25.0±26.1	26.0±23.5	0.99 (0.65 to 1.49)	
Level 2	10.7±11.4	14.3±15.1	0.72 (0.50 to 1.04)	
Level 3	0	0	—	
Participants <18 yr of age — no.	47	21		
Mean number of hypoglycemic events	40.6±36.3	48.2±34.8	0.87 (0.58 to 1.29)	
Level 1	26.2±26.3	28.0±23.5	0.99 (0.62 to 1.57)	
Level 2	11.5±12.0	17.6±16.1	0.64 (0.42 to 0.96)	
Participants ≥18 yr of age — no.	9	7		
Mean number of hypoglycemic events	27.1±31.7	27.0±27.7	1.09 (0.40 to 2.98)	
Level 1	18.8±25.7	20.0±24.2	1.05 (0.32 to 3.47)	
Level 2	6.4±5.9	4.4±3.8	1.33 (0.48 to 3.72)	

* Plus–minus values are means ±SD unless otherwise indicated.

† For insulin use, the treatment effect is shown as the least-squares (LS) mean between-group difference in the change from baseline at week 52 (golimumab minus placebo). For hypoglycemic events, the treatment effect is shown as the ratio of the rate of hypoglycemic events (the number of events per patient-year of exposure) in the golimumab group to that in the placebo group.

‡ P values were calculated with the use of the Hochberg approach to control for multiple comparisons. Additional details are provided in the Supplementary Appendix.

§ Hypoglycemia was defined in the protocol as a biochemically confirmed blood glucose level of 70 mg per deciliter (3.9 mmol per liter) or less, irrespective of clinical symptoms and events related to severe hypoglycemia (with severe hypoglycemia defined as an event characterized by altered mental or physical status [or both] that requires assistance from another person for recovery). Hypoglycemic events were further assessed according to American Diabetes Association levels[27]: level 1 is a blood glucose reading of 54 to less than 70 mg per deciliter (3.0 to <3.9 mmol per liter); level 2, a blood glucose reading of less than 54 mg per deciliter; and level 3, a severe event characterized by altered mental or physical status (or both) that requires assistance from another person for recovery. The analysis of hypoglycemic events according to age group (<18 years or ≥18 years) was performed post hoc.

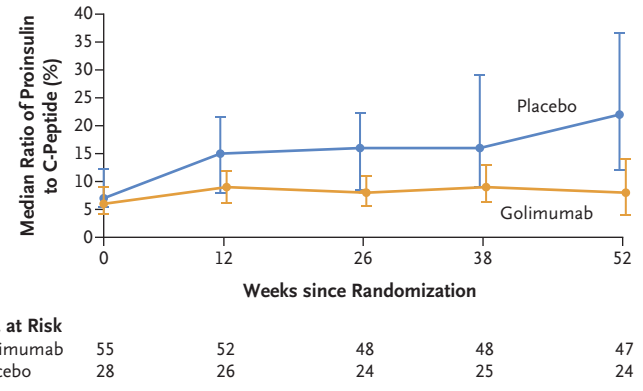

Figure 2. Ratio of Fasting Proinsulin to C-Peptide over Time.

At week 52, the Hodges–Lehmann estimate of the median treatment difference was 0.124 (95% CI, 0.064 to 0.184). I bars indicate interquartile ranges.

the least-squares mean (±SE) change from baseline in the glycated hemoglobin level did not differ significantly between the golimumab group and the placebo group (0.47±0.21% vs. 0.56±0.29%, P=0.80). At week 52, 28 of 56 participants (50%) in the golimumab group and 8 of 28 participants (29%) in the placebo group had a glycated hemoglobin level of less than 7.0%; 35 of 56 (62%) and 12 of 28 (43%), respectively, had a glycated hemoglobin level of less than 7.5% (Table S1).

At baseline, the total daily insulin use was similar in the golimumab group and the placebo group (0.42 U per kilogram per day vs. 0.44 U per kilogram per day), but at week 52, the total daily insulin use was lower in the golimumab group than in the placebo group (0.51 U per kilogram per day vs. 0.69 U per kilogram per day) (Fig. 1C). The increase in insulin use over 52 weeks was less in the golimumab group than in the placebo group (0.07 U per kilogram per day vs. 0.24 U per kilogram per day, P=0.001) (Table 2). At week 52, at total of 7 participants (12%) in the golimumab group and no participants in the placebo group were receiving an insulin dose of 0.25 U per kilogram per day or less.

The mean number of hypoglycemic events through 52 weeks was similar in the golimumab group and the placebo group (38.2 events vs. 42.9 events) (Table 2). However, in post hoc analyses, the mean number of level 2 hypoglycemic events through 52 weeks among those younger than 18 years of age was estimated to be 36% lower in the golimumab group than in the placebo group (11.5 vs. 17.6), and the upper boundary of the 95% confidence interval of the treatment effect (the ratio of the hypoglycemic event rates between the trial groups) was below 1, indicating no effect (Table 2). There were no level 3 events in either group. The mean (±SD) number of daily fingerstick blood glucose assessments per participant was similar in the golimumab group and the placebo group (3.7±1.3 vs. 3.9±1.0).

At week 52, the percentage of participants who had a C-peptide response was 41% in the golimumab group (23 of 56) and 11% in the placebo group (3 of 28), for a between-group difference of 30 percentage points (95% CI, 16 to 51) (Fig. 1D). Even the participants in the golimumab group who did not meet the criteria for a C-peptide response had a numerically higher C-peptide AUC than those in the placebo group. In addition, a partial-remission response was observed in 43% (24 of 56) of the participants in the golimumab group at week 52, as compared with 7% (2 of 28) of the participants in the placebo group, for a between-group difference of 36 percentage points (95% CI, 22 to 55) (Fig. 1E and Fig. S4). Over 52 weeks, the median ratio of fasting proinsulin to C-peptide was stable in the golimumab group, as compared with an increase in the placebo group. At week 52, the Hodges–Lehmann estimate of the median treatment difference was 0.124 (95% CI, 0.064 to 0.184), indicating that the treatment effect was likely to be better with golimumab than with placebo (Fig. 2).

PHARMACOKINETICS AND IMMUNOGENICITY

Trough serum concentrations of golimumab reached steady-state levels after induction therapy and were maintained through week 52. Among the 56 participants in the golimumab group, antibodies to golimumab were detected in 30 (54%), of whom 29 (97%) had antidrug antibody titers of less than 1:1000; among these 29 participants, 12 (41%) had positive results for neutralizing antibodies. The presence of antidrug antibodies was not correlated with efficacy end points or injection-site reactions.

SAFETY END POINTS

A summary of key safety events is provided in Table 3. The incidence of adverse events was 91% (51 of 56 participants) in the golimumab group and 82% (23 of 28) in the placebo group. No

severe or serious infections occurred in either group. Infections were reported in 40 of 56 participants (71%) in the golimumab group and 17 of 28 (61%) in the placebo group; all were mild or moderate (Table S2). The incidence of injection-site reactions was similar in both trial groups. One serious adverse event was reported in each trial group; neither was deemed by trial investigators to be related to the trial regimen nor led to withdrawal from the trial or discontinuation of the trial regimen.

Hypoglycemic events were reported as adverse events at the discretion of the investigators. These events were reported in 13 participants (23%) in the golimumab group and in 2 participants (7%) in the placebo group; none of these events were reported as severe or serious. Of the 13 hypoglycemic adverse events reported in the golimumab group, 7 were reported at a single trial site, which recorded hypoglycemic adverse events in all the participants at the site (including the 2 events in the placebo group); the other 6 hypoglycemic adverse events were reported across five different trial sites.

No cases of diabetic ketoacidosis, neoplasia, serious or opportunistic infections, tuberculosis, or anaphylactic reactions were reported. The percentage of participants who had a postbaseline decrease in the neutrophil count was higher in the golimumab group than in the placebo group (29% [16 of 56 participants] vs. 19% [5 of 27]); transient fluctuations in the neutrophil count were observed among the participants in the golimumab group while they were receiving treatment. Four participants in the golimumab group had neutropenia of grade 3 or 4 according to the Common Terminology Criteria for Adverse Events.[34] One participant who had a low neutrophil baseline count discontinued treatment at 6 months.

Table 3. Adverse Events (Safety Analysis Population).

Adverse Event	Golimumab (N=56)	Placebo (N=28)
	number (percent)	
Any adverse event	51 (91)	23 (82)
Leading to discontinuation*	2 (4)	0
Related to trial agent†	24 (43)	12 (43)
Any serious adverse event‡	1 (2)	1 (4)
Death	0	0
Pregnancy	0	0
Any infection§	40 (71)	17 (61)
Serious infection	0	0
Opportunistic infection	0	0
Active tuberculosis	0	0
Neoplasia	0	0
Hypoglycemia¶	13 (23)	2 (7)
Any injection-site reaction	13 (23)	8 (29)
New or worsening autoimmune disease	0	1 (4)

* One participant in the golimumab group was withdrawn from the trial on day 113 because of pain at the injection site, and another patient in the golimumab group was withdrawn on day 183 because of intermittent leukopenia and neutropenia that was deemed to be possibly related to the trial drug. The latter participant also had low white-cell counts at baseline.
† An adverse event related to the trial agent was defined as any event that was deemed by the trial investigators to be very likely, probably, or possibly related to the trial drug or placebo or if the data regarding the relationship to the trial agent were missing.
‡ One participant in the golimumab group had diplopia due to an orbital floor fracture after an automobile accident, and one participant in the placebo group had cholelithiasis and underwent ambulatory cholecystectomy. Both events were reported to have resolved and were not deemed by trial investigators to be related to golimumab or placebo; the patients did not discontinue their assigned regimen because of these adverse events.
§ Additional information regarding the types of infections is provided in Table S2.
¶ Hypoglycemic events were reported as adverse events at the discretion of the investigators.

DISCUSSION

In this phase 2 trial involving children and young adults with newly diagnosed overt type 1 diabetes, golimumab resulted in better endogenous insulin production than placebo, as indicated by the 4-hour C-peptide AUC. Even small effects on C-peptide levels have been previously reported to be related to better short-term and long-term outcomes, such as reductions in hypoglycemia, neuropathy, and retinopathy.[35]

Although glycemic control in children and young adults with type 1 diabetes can be very challenging, both groups in our trial had better glycemic control than that reported in patients with type 1 diabetes in the general population.[5] The participants in the golimumab group generally attained this level of glycemic control with significantly less insulin therapy than those in the placebo group.

In addition, 41% of the participants in the golimumab group had an increase or not more than a 5% decrease in C-peptide AUC through week 52. Moreover, although there was no dif-

ference between the groups in mean glycated hemoglobin levels, our findings suggest that golimumab was associated with increases and longer times in partial remission, also known as the "honeymoon period," as indicated by the insulin dose-adjusted glycated hemoglobin level, which includes both insulin use and glycated hemoglobin level in the calculation. This period is clinically relevant because patients can more easily achieve glycated hemoglobin goals with lower insulin doses.[28] Furthermore, the ratio of fasting proinsulin to C-peptide, an established measure of beta-cell stress and dysfunction,[36] was largely unchanged among the participants who received golimumab but increased over time among the participants who received placebo, a finding that suggests improved beta-cell health.

The role of TNF-α in type 1 diabetes has been unclear in preclinical studies.[18-22] Our trial results are consistent with those of a phase 1 trial of etanercept, another TNF-α–blocking drug, involving children with type 1 diabetes, in which the C-peptide level increased and insulin use decreased.[37]

TNF-α blockers are approved for patients as young as 2 years of age who have autoimmune conditions, and these drugs have established risk-to-benefit profiles.[25,38-41] We used a specific golimumab dosing regimen for type 1 diabetes that had a safety profile consistent with previously used golimumab regimens. The percentage of participants in whom antibodies to golimumab were detected and the predominance of low-titer antidrug antibodies were also consistent with those reported in other studies of golimumab that used enzyme immunoassays.[30,42] Future efforts will be needed to determine the extent of beta-cell preservation and how to improve golimumab efficacy.

Our trial has some limitations that are consistent with phase 2 trials — a small number of participants and participants with a limited number of coexisting conditions studied. Thus, effects beyond those in the population studied, especially concerning age and race, cannot be adequately inferred. Information about continuous insulin infusion or continuous glucose monitoring was not collected; thus, the effect of those methods on the results cannot be assessed.

Among children and young adults with newly diagnosed overt type 1 diabetes, golimumab resulted in better endogenous insulin production and less exogenous insulin use than placebo.

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APPENDIX

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