Imatinib therapy for patients with recent-onset type 1 diabetes: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

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Summary

Background Type 1 diabetes results from autoimmune-mediated destruction of β cells. The tyrosine kinase inhibitor imatinib might affect relevant immunological and metabolic pathways, and preclinical studies show that it reverses and prevents diabetes. Our aim was to evaluate the safety and efficacy of imatinib in preserving β-cell function in patients with recent-onset type 1 diabetes.

Methods We did a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Patients with recent-onset type 1 diabetes (<100 days from diagnosis), aged 18–45 years, positive for at least one type of diabetes-associated autoantibody, and with a peak stimulated C-peptide of greater than 0·2 nmol L^{-1} on a mixed meal tolerance test (MMTT) were enrolled from nine medical centres in the USA (n=8) and Australia (n=1). Participants were randomly assigned (2:1) to receive either 400 mg imatinib mesylate (4×100 mg film-coated tablets per day) or matching placebo for 26 weeks via a computer-generated blocked randomisation scheme stratified by centre. Treatment assignments were masked for all participants and study personnel except pharmacists at each clinical site. The primary endpoint was the difference in the area under the curve (AUC) mean for C-peptide response in the first 2 h of an MMTT at 12 months in the imatinib group versus the placebo group, with use of an ANCOVA model adjusting for sex, baseline age, and baseline C-peptide, with further observation up to 24 months. The primary analysis was by intention to treat (ITT). Safety was assessed in all randomly assigned participants. This study is registered with ClinicalTrials.gov, NCT01781975 (completed).

Findings Patients were screened and enrolled between Feb 12, 2014, and May 19, 2016. 45 patients were assigned to receive imatinib and 22 to receive placebo. After withdrawals, 43 participants in the imatinib group and 21 in the placebo group were included in the primary ITT analysis at 12 months. The study met its primary endpoint: the adjusted mean difference in 2-h C-peptide AUC at 12 months for imatinib versus placebo treatment was 0·095 (90% CI −0·003 to 0·191; p=0·048, one-tailed test). This effect was not sustained out to 24 months. During the 24-month follow-up, 32 (71%) of 45 participants who received imatinib had a grade 2 severity or worse adverse event, compared with 13 (59%) of 22 participants who received placebo. The most common adverse events (grade 2 severity or worse) that differed between the groups were gastrointestinal issues (six [13%] participants in the imatinib group, primarily nausea, and none in the placebo group) and additional laboratory investigations (ten [22%] participants in the imatinib group and two [9%] in the placebo group). Per the trial protocol, 17 (38%) participants in the imatinib group required a temporary modification in drug dosing and six (13%) permanently discontinued imatinib due to adverse events; five (23%) participants in the placebo group had temporary modifications in dosing and none had a permanent discontinuation due to adverse events.

Interpretation A 26-week course of imatinib preserved β-cell function at 12 months in adults with recent-onset type 1 diabetes. Imatinib might offer a novel means to alter the course of type 1 diabetes. Future considerations are defining ideal dose and duration of therapy, safety and efficacy in children, combination use with a complimentary drug, and ability of imatinib to delay or prevent progression to diabetes in an at-risk population; however, careful monitoring for possible toxicities is required.

Funding Juvenile Research Diabetes Foundation.

Introduction

Type 1 diabetes results from the autoimmune destruction of insulin-producing β-cells.[1] Although exogenous insulin is widely available, affected individuals cannot consistently achieve euglycaemia with current formulations and technologies, and as a result remain at risk of acute and long-term complications.[2] Thus, preserving the function of remaining β cells, before or after diagnosis, offers the

Lancet Diabetes Endocrinol 2021

Published Online
June 29, 2021
https://doi.org/10.1016/S2213-8587(21)00139-X

See Online/Comment
https://doi.org/10.1016/S2213-8587(21)00169-8

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Research in context

Evidence before this study

A series of clinical trials have been done in recent-onset type 1 diabetes in an attempt to preserve β-cell function, primarily with immunotherapies and often targeting T cells; some of these efforts have had modest initial success, but without robust durable effects. We searched PubMed for articles published in any language from database inception up to Dec 1, 2020, with the search terms imatinib, tyrosine kinase inhibitor, diabetes, and autoimmunity. We found preclinical and clinical studies suggesting that imatinib might target both immunological and metabolic pathways, and provide a novel way to treat type 1 diabetes. Several preclinical studies in rodent models suggest that imatinib has effects on β-cell function and insulin sensitivity. Furthermore, case reports and case series suggest benefits of imatinib in treating some autoimmune diseases, and beneficial effects in type 1 and type 2 diabetes.

Added value of this study

To our knowledge, this trial is the first phase 2 study of a tyrosine kinase inhibitor in recent-onset type 1 diabetes, utilising the first-in-class drug member imatinib. This study showed that 26 weeks of treatment with imatinib slowed the decrease in β-cell function for up to 12 months, although the effect was not sustained out to 24 months. Secondary and exploratory analyses did not reveal overt effects of this treatment on immune responses, but did indicate a series of unique effects on metabolism, with improved β-cell function and insulin sensitivity. The most common safety issues associated with imatinib use included gastrointestinal issues (primarily nausea that was self-limited and transient) and additional laboratory issues (associated with changes in liver function tests and abnormal complete blood cell counts). In general, imatinib was well tolerated, and if participants did develop adverse events, they tended to occur early in the course of drug administration, to be milder than that described in the oncology literature, and usually resolved in the ensuing days and weeks with ongoing therapy.

Implications of all the available evidence

Imatinib might offer unique benefits to patients with type 1 diabetes and provide a novel means to target β-cell health and insulin sensitivity; however, treated participants should be monitored closely for potential side-effects and toxicities that require modification to imatinib dosing. Possible future studies with imatinib in type 1 diabetes could explore lower doses and longer durations of therapy; extend related studies to children and adolescents; assess imatinib in a population at risk of type 1 diabetes to delay or prevent progression to disease; and assess imatinib in combination with drugs that work by complimentary mechanisms, such as one of the previously successful and more traditional immunotherapies.

best means to control the disease process. We and others have done a series of clinical trials with various immunotherapies aimed at preserving β-cell function in people with recent-onset type 1 diabetes. Despite these research efforts, there has not been robust success: a small number of large, placebo-controlled, phase 2 studies met their primary endpoint, but treated patients must usually remain on exogenous insulin, and the effects of immunotherapies wane with time as the therapies are withdrawn.[3–8]

Therefore, investigators continue to search for novel therapies to stop β-cell destruction, with particular attention on repurposing drugs that are already approved for other indications, thereby accelerating their application to type 1 diabetes. In this search, a focus has been on imatinib mesylate (brand name Gleevec), a first-in-class tyrosine kinase inhibitor that has had notable success as a therapy for chronic myelogenous leukemia,[9] and that might also affect both immunological and metabolic pathways. In preclinical studies, imatinib has been shown in non-obese diabetes (NOD) mice to prevent diabetes and induce remission of recent-onset diabetes without requiring continuous ongoing therapy.[10,11] Anti-CD3 monoclonal antibody and anti-thymocyte globulin have had similar effects in NOD mice, with promising effects when evaluated in clinical trials.[3,5] Further preclinical investigation suggests that imatinib might act, at least in part, via novel metabolic pathways, such as counteracting high levels of endoplasmic reticulum (ER) stress in β cells and reducing apoptosis, and improving insulin sensitivity.[10,12–14]

These preclinical observations have been extended to the clinical setting, in which case reports and case series have shown positive effects of imatinib in patients with autoimmune conditions (such as rheumatoid arthritis[15]) and patients with either type 1 or type 2 diabetes.[16] To explore the role of imatinib in the preservation of β-cell function in type 1 diabetes, we did a phase 2 trial with imatinib in patients with recent-onset disease, and report the efficacy and safety results herein for patients followed up for 24 months.

Methods

Study design and patients

We did a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Screening, enrolment, and subsequent study visits occurred at nine medical centres in the USA (n=8) and Australia (n=1; appendix p 16). Eligible participants were people aged 18–45 years at the time of screening; less than 100 days from diagnosis at the time of enrolment; positive for at least one type of diabetes-associated autoantibody (microassayed insulin antibodies, tested only if duration of insulin therapy was <10 days; or GAD-65 antibodies,

ICA-512 antibodies [also known as IA-2], ZnT8 antibodies, or islet-cell autoantibody [also known as ICA]); and had a peak stimulated C-peptide of greater than 0·2 nmol L^{-1} during a mixed meal tolerance test (MMTT). Exclusion criteria at screening were signs of chronic active infection (eg, hepatitis, tuberculosis, cytomegalovirus, Epstein-Barr virus, or toxoplasmosis), or screening laboratory evidence consistent with a chronic active infection (such as positivity for HIV, a positive purified protein derivative or interferon-γ release assay suggestive of tuberculosis, or positivity for hepatitis B surface antigen; acute infections had to be resolved before treatment could commence); past cardiac disease (congestive heart failure, myocardial infarction, arrhythmia, or structural defects or suspicion of structural defects; anaemia (less than the lower limit of normal at each participating site), leukopenia (<3000 leukocytes per μL), thrombocytopenia (<125 000 platelets per μL), or neutropenia (<1500 neutrophils per μL); history of anaphylaxis, angio-oedema, or serious cutaneous drug reactions; liver dysfunction (alanine aminotransferase or aspartate aminotransferase >2·0 times the upper limit of normal persistent for 1 week or longer) or renal dysfunction (serum creatinine >1·2 times the upper limit of normal in two tests ≥1 week apart); clinically significant metabolic bone disease (except adequately treated rickets); anticipated ongoing use of diabetes medications other than insulin; previous or current treatment known to cause an ongoing change in the course of type 1 diabetes or immunological status (eg, high-dose inhaled, extensive topical, or systemic glucocorticoids); previous treatment with imatinib or related tyrosine kinase inhibitor; inability to avoid medications that affect cytochrome P450 3A4, or use of drugs that interact with imatinib leading to altered plasma concentrations of the drugs; for women, pregnancy or breastfeeding, less than 100 days post partum before enrolment, or unwilling to defer pregnancy during the 2-year study period; known coagulation disorders or use of anticoagulants; any condition that, in the investigator's opinion, might compromise study participation or confound interpretation of the results; and, at the time of randomisation, signs of QT prolongation on electrocardiogram (>450 ms in men and >470 ms in women). All participants had to consent to use reliable and effective forms of contraception, for women during the entire 2-year trial period, and for men up to 3 months after the study drug dosing period.

The trial was done according to the Declaration of Helsinki and in accordance with Good Clinical Practice guidelines, under an investigational new drug application (US Food and Drug Administration [FDA] application number IND 117644) and was approved by the independent institutional review boards at each participating centre. All participants provided written informed consent. The study protocol is available online. Safety was regularly reviewed by an independent data and safety monitoring board (DSMB).

For the **study protocol** see https://www.protocols.io/view/collection-of-protocols-and-guidelines-for-safety-bvfqn3mw

Randomisation and masking

Participants were enrolled by the study coordinator or other member of the trial group at each site after approval by the site principal investigator or co-investigator. Eligible patients were randomly assigned (2:1) to receive imatinib or placebo. A site-stratified randomisation scheme was computer generated at a central data coordinating centre (University of South Florida, Tampa, FL, USA) with permuted blocks of size 6. The system provided a unique identifier for each new participant, and site personnel randomly assigned patients via an interactive web-based randomisation system, which sent the treatment assignments directly to unmasked pharmacists at each of the nine clinical sites. All investigators, site personnel, and participants were masked to study group assignment for the duration of the study, and were unmasked after all participants had completed the 24-month follow-up.

Procedures

The imatinib group received imatinib mesylate as 4×100 mg film-coated tablets per day for 26 weeks, and the placebo group received matching tablets (Novartis, East Hanover, NJ, USA). Dose selection was based on a combination of extrapolation from preclinical studies, the starting dose in oncology settings, and reported benefits in patients with other autoimmune diseases.[9,15,17] Pill counts at each study visit were used to assess participant adherance to the medication. Study drug administration was modified, as necessary, according to clinical symptoms or laboratory abnormalities, on the basis of algorithms derived from oncology settings. Briefly, for adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0) of grade 2 severity or worse and considered likely to be related to imatinib, including gastrointestinal issues (eg, nausea, vomiting, or diarrhoea), muscle cramping, oedema, skin rash, or laboratory abnormalities (eg, liver function changes and myelosuppression) the study drug or placebo dose was reduced by 50% until the issue resolved. Grade 3 events prompted discontinuation of study drug or placebo until the issue resolved, with rechallenge thereafter. Recurrent persisting grade 3 adverse events resulted in drug or placebo termination, with patient observation continued throughout the remainder of the trial. MMTTs were done at screening (baseline), 3, 6, 12, 18, and 24 months (4-h tests at baseline, 12 and 24 months, and 2-h tests at other timepoints), with measurement of glucose, C-peptide, and insulin. The full schedule of assessments is provided in the appendix (pp 17–19).

All participants received intensive diabetes management, and glycated haemoglobin (HbA_{1c}) was assessed

every 3 months to evaluate metabolic control. Participants were expected to take a sufficient number of insulin injections per day or to utilise continuous subcutaneous insulin infusion with the aim of achieving the HbA_{1c} target (≤7·0%) and glycaemic targets (preprandial plasma glucose 90–130 mg/dL, postprandial plasma glucose 180 mg/dL, and bedtime plasma glucose 110–150 mg/dL) recommended by the American Diabetes Association. Participants were encouraged to monitor blood glucose at least four times per day with a glucometer, and some elected to use continuous glucose monitoring. Per study protocol, a reportable hypoglycaemic event was defined as events resulting in loss of consciousness, seizure, or requiring assistance of others due to altered state of consciousness. A hyperglycaemic event was an event resulting in diabetic ketoacidosis. Insulin usage data was collected by participants in insulin use logs for the preceding 5 days before study visits.

Biochemical autoantibodies were measured at the Barbara Davis Center (Aurora, CO, USA) with radioimmunobinding assays, and islet cell autoantibodies were measured at the University of Florida, as described previously.[5] C-peptide, HbA_{1c}, proinsulin, adiponectin, and serum chemistries were measured at the Northwest Lipid Research Laboratory (Seattle, WA, USA). β-cell death was assayed as described previously.[18] All other routine laboratory measures were done locally.

Lymphocyte and myeloid cell subsets were evaluated from frozen peripheral blood mononuclear cells (PBMCs) isolated from whole blood and viably cryopreserved at the Immune Tolerance Network Core facility, as outlined previously.[5] Samples were assessed with multicolour flow cytometry (antibody panel configuration shown in the appendix, pp 8–9) in a LSRFortessa Flow Cytometer (BD Biosciences, Franklin Lakes, NJ, USA) with manual sequential gating performed in FlowJo version 9.9.6 (BD Biosciences).

See Online for appendix

All data were captured, managed, maintained, and retrieved on an Oracle database management system. Clinical data were entered via web-based forms. Data checks were done at the central data coordinating centre at regular intervals with questions or issues communicated back to the clinical sites for correction or clarification.

Outcomes

As a measure of endogenous insulin secretion, the primary endpoint was the difference in the area under the curve (AUC) mean for stimulated C-peptide in the first 2 h of a 4-h MMTT at the month 12 visit in the imatinib group versus the placebo group. Samples from MMTT were sent for central assessment. Prespecified secondary outcomes included the 2-h C-peptide AUC mean at 24 months; 4-h C-peptide AUC mean at 12 months and 24 months; 2-h C-peptide AUC mean longitudinally up to 24 months; exogenous insulin use at 12 months and 24 months; major hypoglycaemic events; HbA_{1c} levels at 12 months and 24 months; and frequency and severity of adverse events in the imatinib group versus placebo group, with comparison of all grade 2 severity or worse adverse events between the groups. Prespecified exploratory endpoints included proportion of participants who were exogenous insulin free (for ≥3 months) with an HbA_{1c} level of 6·5% or less at 12 months and 24 months; fasting proinsulin to C-peptide ratios; adiponectin concentrations; autoantibody titres and other immunological measures (eg, immune cell phenotyping by flow cytometry, and post-hoc analysis of non-inflammatory immune cell subsets in the upper *vs* lower quartile of C-peptide AUC responders based on AUC mean); β-cell glucose sensitivity and insulin sensitivity (calculated from MMTT glucose, C-peptide, and insulin data, as described previously[19,20]); and β-cell apoptosis calculated from the β-cell death assay.[18] We intended to measure glucagon but collected samples were inappropriate for analysis.

Study personnel assessed adverse events and the use of concomitant medications throughout the study. Adverse events were communicated to the central coordinating centre. They were graded in terms of severity according to the common toxicity criteria or study-specific criteria and the investigator made a determination as to the relation to therapy. An adverse event case report form was completed for all adverse events of grade 2 or worse severity regardless of relationship to therapy. For reporting of serious adverse events, the MedWatch Form of the FDA was also completed and sent to the central coordinating center within 24 h of site notification of the event. Serious adverse events were reviewed by the study safety monitoring committee, and the DSMB as appropriate. Deaths were reported immediately. Event outcome and other follow-up information regarding treatment and resolution were obtained and reported when available, if not known at the time the event was reported. The follow-up information had to contain sufficient detail to allow for a complete medical assessment of the case and an independent determination of possible causality. Adverse events were assessed by the study designated medical monitor. The DSMB did regular safety reviews approximately every 3–6 months (and, as needed) of adverse events by treatment group assignment. Any adverse events leading to treatment discontinuation were reviewed by the DSMB.

Statistical analysis

With use of standard equations for the comparison of two means, a sample size of 40 participants treated with imatinib and 20 treated with placebo who had the primary endpoint C-peptide AUC measurement would provide 85% power to detect a 35% increase in the expected imatinib group mean (0·551 *vs* 0·744, ng/L scale; 0·439 *vs* 0·556 on the transformed scale. This calculation was based on a two-sample *t* test at the 0·05 α level (one-sided) with 2:1 allocation. To address missing data on the primary endpoint, the target sample size was set at 66 participants (44+22), allowing for as many as

10% of participants without a 12-month MMTT C-peptide AUC measurement. Full details on sample size and power calculation are provided in the appendix (p 14).

The primary endpoint analysis compared the difference between the treated group versus the placebo group in the 2-h C-peptide AUC mean at 12 months, with use of an ANCOVA model adjusting for sex, baseline age, and baseline C-peptide to obtain mean difference. The primary and secondary analyses were based on a prespecified intention-to-treat (ITT) cohort, defined as all randomly assigned participants with the required C-peptide measurement regardless of treatment adherence. Any individuals who stopped therapy were encouraged to continue to follow the protocol in terms of outcome assessments. The AUC mean was calculated applying the trapezoidal rule (base measured in min) to six timed C-peptide values (collected at 0, 15, 30, 60, 90, and 120 min) and dividing by 120 min. The AUC mean was transformed with the function: $\ln(y_{C\text{–peptide}}+1)$, where $y_{C\text{-petide}}$ represents AUC mean, to provide improved normal distributional shape by the test statistic. The treatment group comparison was based on a Wald test with the ANCOVA model at the 0·05 α level (one-sided). Mean difference confidence intervals (CIs) were calculated with the bootstrap method. The adjusted means for the CIs for each treatment group were determined as the means of the other covariates. This same model was used for secondary C-peptide AUC measurements, insulin use, HbA_{1c} levels, serum adiponectin, ratio of fasting proinsulin to C-peptide, and the autoantibody titre values. The transformation applied to these endpoints varied to maintain approximately normally distributed residuals (appendix p 16). For analysis of HbA_{1c} levels a single outlier was removed because it violated the normal residual requirement of the model. For the proinsulin to C-peptide ratios, no transformation was adequate without removing five outliers. When removing the five outliers (one at 3 months, two at 6 months, and two at 12 months), the residuals were normalised. To assess treatment effect without removing the outliers we took the residuals from the ANCOVA model after adjusting for the baseline value, age, and sex, and applied a two-sample Wilcoxon test for treatment group difference. Only the C-peptide values are reported with one-sided 90% CIs; all other significance levels are two-sided with corresponding 95% CIs. These analyses were done with TIBCO Spotfire S+ software (version 8.2.0). To determine if the placebo group had the expected change in C-peptide AUC during the first 12 months of the study, we also compared the observed changed in C-peptide AUC in the placebo group to pooled data from placebo groups from previous recent-onset type 1 diabetes trials in TrialNet.[21]

Although an interim analysis had been planned, due the small sample size and limited data during the conduct of the trial, the DSMB did not feel that an interim analysis was necessary and thus it was not done. All individuals who were randomly assigned in the study were included in the safety analysis.

Exploratory and supplemental outcome measurements were analysed with a mixed model for repeated measures (MMRM). These outcomes included 2-h plasma glucose AUC, 2-h insulin secretion AUC, β-cell glucose sensitivity, weight, BMI, long and short acting insulin doses, fasting plasma glucose and insulin secretion, and insulin sensitivities. The same model was applied to immune cell subsets. MMRM included study visits, treatment group, and interaction of treatment group by visits as fixed effects, and baseline measurements as covariates. A compound symmetry variance–covariance structure was applied to model within-patient random effects. p values were then calculated to compare the differences of least square means between the imatinib group versus the placebo group at each study visit cross-sectionally. Multiple testing correction was made to the p values across the multiple visits. R software (version 4.0.3) and the nlme package were used for the MMRM analyses. Not all supplemental analyses proposed in the study protocol are presented herein, due to a change in priority of analyses. Additionally, some immunological analyses are ongoing. This study is registered with ClinicalTrials.gov, NCT01781975.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 12, 2014, and May 19, 2016, we screened 80 individuals, of whom 67 were enrolled and randomly allocated to receive imatinib (n=45) or placebo (n=22; figure 1). Demographic and baseline characteristics were similar between the two groups, with the exception of somewhat higher weight and BMI in the imatinib group (table 1). Adherence with the study protocol was high, with only two participants in the imatinib group and one participant in the placebo group withdrawn before the primary endpoint assessment at 12 months (figure 1). Thus, 64 participants were included in the primary ITT analysis at 12 months. A further two participants in the imatinib group withdrew before 24 months. Adherence to study drug or placebo was also high. With complete adherence to the 4 pills ingested every day for 26 weeks defined as 1·00, median pill consumption in the imatinib group was 0·88 (IQR 0·76–0·93; range 0·09–1·00) and 0·97 (0·86–1·00; 0·29–1·00) in the placebo group. These calculations did not account for adjustments to drug dosing mandated per the trial protocol for adverse events.

For the ITT population, we summarised the adjusted C-peptide AUC means for the study groups during follow-up from baseline to 24 months (figure 2, appendix p 10). For the primary endpoint of 2-h C-peptide

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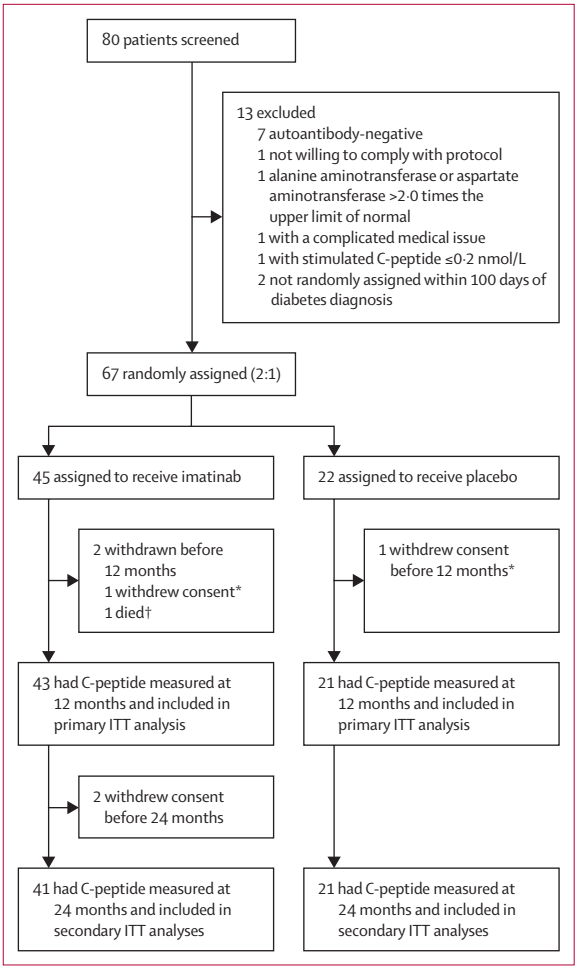

Figure 1: **Trial profile**
ITT=intention to treat. *Reasons multifactorial (including some possible side-effects that the participant attributed to study drug and life circumstances; both in the first 6 months of the study during drug or placebo administration). †74 days after completion of drug administration.

AUC mean in response to a 4-h MMTT at 12 months, the mean estimate was 0·583 nmol L^{-1} (90% CI 0·529–0·639) for the imatinib group and 0·489 nmol L^{-1} (0·417–0·564) for the placebo group (figure 2). The adjusted mean difference between study groups was 0·095 (90% CI –0·003 to 0·191), and constituted a 19·4% treatment effect (difference in the adjusted 12-month means divided by the placebo group mean). The 12-month group values for 2-h C-peptide AUC mean were compared within the ANCOVA model and were significantly different, with a Wald's Z value from the model of 1·66 (p=0·048, one-tailed). No marked effect was observed at the later assessments up to 24 months (figure 2). Data on 4-h C-peptide AUC mean were consistent with the 2-h analyses: at 12 months, the model-adjusted mean was 0·581 nmol L^{-1} (90% CI 0·528–0·635) for the imatinib group and 0·479 nmol L^{-1} (0·409–0·553) for the placebo group (p=0·048; one-sided; appendix p 10). We also evaluated whether the placebo group had an expected decrease in C-peptide with time, and, based on a model that used TrialNet data, the 12-month C-peptide AUC means (2-h and 4-h) for the placebo group decreased as expected.[21]

In other secondary analyses, exogenous insulin use was similar at baseline between the two groups, but was used at notably lower doses in the imatinib group versus the placebo group at the first follow-up assessment at 3 months. This difference persisted at the 6 month assessment (6-month mean difference –0·137 units per kg [95% CI –0·260 to –0·0458]), with no difference thereafter (figure 3A, appendix p 10). Short-acting insulin use was responsible for most of the group difference (appendix p 11). Body weight and BMI did not change appreciably during the 24-month study period in either group (appendix p 11). For glycaemic control during the study, both groups were treated to the same HbA_{1c} target of 7·0% or less. HbA_{1c} initially decreased lower than baseline levels in both groups, and was lower in the imatinib group than in the placebo group during the active treatment phase, with the greatest difference at 3 months (mean difference –0·422% [95% CI –0·772 to –0·068]; figure 3B, appendix p 10).

In exploratory analyses of data from MMTTs, fasting plasma glucose concentrations and fasting insulin secretion rates were similar between the imatinib and placebo groups at baseline and did not differ thereafter (appendix p 11). By contrast, the MMTT-stimulated responses showed distinct differences between the imatinib and placebo groups during the treatment period (figure 4, appendix p 1). The difference was most notable for 2-h glucose concentration, which was decreased in the imatinib group at 3 months (mean difference –2·74 mmol L^{-1} [95% CI –1·17 to –4·07] and 6 months (mean difference –4·10 mmol L^{-1} [–2·30 to –5·62]) compared with values in the placebo group (figure 4A). Despite the difference in glucose excursion, the 2-h insulin secretion AUC was similar between the imatinib and placebo groups during the active treatment period and up to 24 months (figure 4B). Consequently, dose-response curves for insulin secretion and plasma glucose were flatter in the placebo group than in the imatinib group (figure 5A). β-cell glucose sensitivity, as the slope of the dose-response function for insulin secretion and plasma glucose,[19] notably increased with imatinib treatment to higher than baseline level at 3 months, and stabilised up to 6 months, but decreased thereafter when participants were off active treatment. By contrast, the measure steadily decreased in the placebo group with time (mean difference at 6 months, 9·4 pmol min^{-1} m^{-2} $mmol^{-1}$ L^{-1} [95% CI 2·23–21·5]; figure 5B). In accordance with the notion that lower glucose concentrations stimulated greater insulin release during imatinib treatment, insulin secretion rates calculated at matched glycaemia (7 mmol L^{-1}) were markedly higher in the imatinib group than in the placebo group at 6 months

(mean difference 23·2 pmol min^{-1} m^{-2} [95% CI 4·3–53·8]; appendix p 11). Insulin sensitivity was estimated on the basis of plasma glucose and insulin measured during the MMTTs. Insulin sensitivity was similar in the two groups at baseline, and remained stable in the imatinib group during active therapy, but decreased in the placebo group (mean difference at 6 months 1·2 mL min^{-1} kg^{-1} [95% CI 0·6–1·8]). This difference resolved off of active therapy at 12 months (appendix p 11).

Additional exploratory analyses were done to investigate possible mechanisms of imatinib action on metabolism. With the effects noted on β-cell glucose sensitivity, and a possible direct effect of imatinib on β-cell function and survival indicated in animal models,[10,12] we evaluated changes in proinsulin to C-peptide ratios with time. No difference was noted in the fasting pro-insulin to C-peptide ratios between the imatinib and placebo groups. However, due to outliers when calculating the ratio, we did a non-parametric test on the treatment group difference and noted a statistically significant difference between the groups during active therapy, with a lower ratio in the imatinib group at both the 3-month assessment (p=0·039) and 6-month assessment (p=0·027; figure 6A). To identify if imatinib therapy had an effect on β-cell apoptosis, we evaluated change in β-cell death with time, using a PCR-based assay for cell-free preproinsulin gene (*INS*; appendix p 2).[18] Low amounts of unmethylated *INS* were noted at baseline in the imatinib group, and we observed no notable change with time in unmethylated or methylated *INS*, or in the ratio of unmethylated to methylated *INS*, compared with baseline and the placebo group. Considering the effect of imatinib on insulin sensitivity, we measured serum adiponectin concentrations. Adiponectin markedly increased in the imatinib group during the 6 months on therapy, compared with in the placebo group (mean difference at 6 months 5·75 mg mL^{-1} [95% CI 2·89–8·59]); by 12 months, adiponectin concentration in the imatinib group had decreased to baseline levels and was similar to mean concentration in the placebo group (figure 6B).

As imatinib has been reported to affect various immune cell types, we did comprehensive immune phenotyping during the course of the study. No statistically significant changes in immune system B cell function in terms of autoantibody titres were noted with time in the imatinib group versus the placebo group (appendix pp 3–4). Immune phenotyping by flow cytometry indicated no substantial differences in B cells, T cells, or myeloid cells between the imatinib and placebo groups (appendix p 5). In further analyses, we noted a transient reduction in the frequencies of $CD141^+$ dendritic cells (known as cDC1) and $CD95^+IgD^-CD27^+$ memory B cells with imatinib, as compared with baseline and placebo group frequencies (appendix p 6), suggesting an effect on rare and metabolically active cells. In evaluating non-inflammatory immune cell subsets in the upper quartile versus lower quartile of C-peptide AUC responders in the imatinib group, we did not observe any differences during the course of the study (appendix p 7). Additional exploratory immunological analyses are ongoing.

	Imatinib group (n=45)	Placebo group (n=22)
Age, years	26·6 (22·4–32·4; 19·0–45·7)	23·4 (21·6–29·9; 18·8–40·6)
Sex		
Male	27 (60%)	10 (45%)
Female	18 (40%)	12 (55%)
Race		
White	44 (98%)	21 (95%)
Black	0	1 (5%)
Asian	1 (2%)	0
Ethnicity		
Non-Hispanic	43 (96%)	19 (86%)
Hispanic	2 (4%)	3 (14%)
Autoantibodies		
GAD-65	39 (87%)	20 (91%)
ICA-512	28 (62%)	15 (68%)
Microassayed insulin	23 (51%)	13 (59%)
Islet-cell autoantibody	24 (55%)*	14 (64%)
ZnT8	22 (49%)	12 (55%)
Number of autoantibody types		
1	9 (20%)	4 (18%)
2	7 (16%)	4 (18%)
3	12 (27%)	1 (5%)
4	8 (18%)	6 (27%)
5	9 (20%)	7 (32%)
Time from diagnosis to first infusion, days	82 (70–91)	84 (73–96)
Weight, kg	73·4 (66·6–80·5)	65·3 (59·6–79·5)
BMI, kg/m^2†	24·1 (22·1–26·0)	22·3 (20·1–25·1)
2-h C-peptide area under the curve mean at baseline	0·736 (0·544–1·000)	0·679 (0·614–0·877)
Glycated hemoglobin at baseline, %	7·4 (6·6–8·1)	7·1 (5·9–8·8)
Total daily insulin dose at baseline, U/kg	0·248 (0·112–0·403)	0·242 (0·154–0·374)

Data are n (%), median (IQR; range), or median (IQR). BMI=body-mass index. *One patient missing data on islet-cell autoantibody status. †Higher BMI in the imatinib group was due to the difference in weight distribution between the groups.

Table 1: **Baseline demographic and laboratory characteristics of participants**

32 (71%) patients who received imatinib and 13 (59%) who received placebo had at least one adverse event of grade 2 severity or worse during the study (appendix p 12). The distribution of adverse events across the grading levels was similar between the groups, with most rated as mild to moderate in severity. However, when evaluating the adverse events deemed likely to be attributable to study drug, a substantially higher proportion of participants in the imatinib group had probable drug-related adverse events, with most events in the mild to moderate categories. Considering all treatment-emergent adverse events of grade 2 severity or worse, notable differences between study groups occurred with gastrointestinal issues (six [13%] participants in the imatinib group *vs* none in the placebo group;

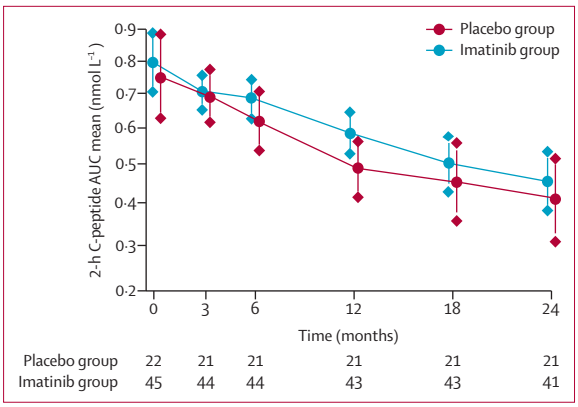

Figure 2: **C-peptide AUC mean responses to MMTT**
2-h C-peptide AUC mean with 90% CIs were obtained from 4-h mixed meal tolerance tests over the study period. Values represent the ITT population with available data at each timepoint. The scale is non-linear under the transformation ln(C-peptide + 1). AUC=area under the curve.

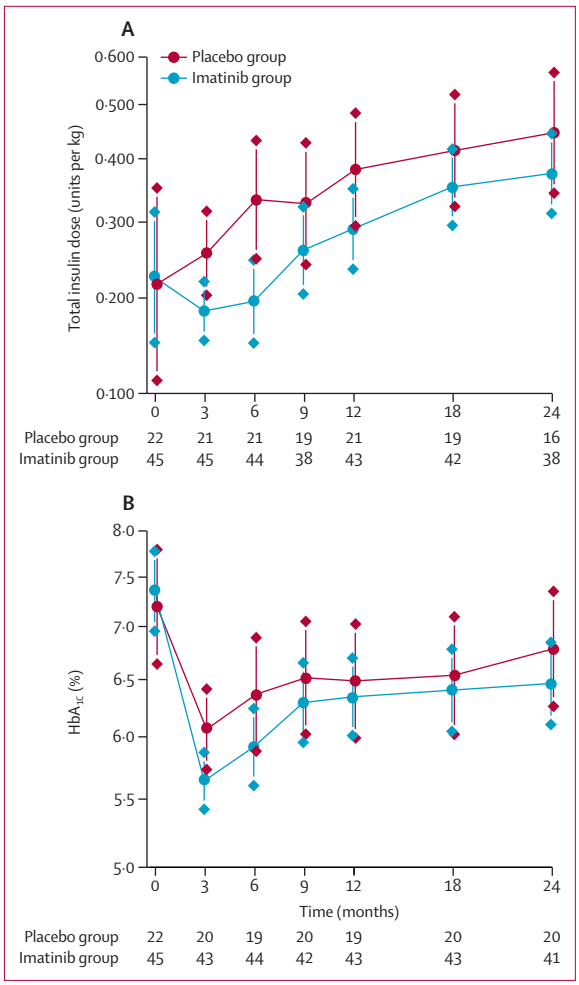

Figure 3: **Insulin use and and HbA_{1c} levels**
n is number of patients with available data. (A) Mean exogenous insulin use per kg of body weight and 95% CIs; non-linear scale under the transformation ln(insulin use + 0·25). (B) Mean HbA_{1c} levels and 95% CIs; non-linear scale under the transformation ln (HbA_{1c}). HbA_{1c}=glycated hemoglobin.

primarily nausea that was self-limited and transient) and additional laboratory investigations (ten [22%] participants in the imatinib group *vs* two [9%] in the placebo group; primarily per protocol assessments to evaluate and track abnormal complete blood cell counts and liver function tests; table 2). Infections and infestations were reported in 12 (27%) imatinib-treated participants versus four (18%) placebo-treated participants. No opportunistic infections were noted, and all infections were confined to grade 2 severity, with the exception of one (2%) participant with grade 3 skin infection in the imatinib group. In terms of adverse events related to diabetes management, one participant in each group had severe hypoglycaemia, and one participant in the placebo group had a single episode of diabetic ketoacidosis.

In evaluation of higher grade adverse events, a single grade 5 adverse event (death) occurred in the imatinib group, which was due to an acute asthma exacerbation from a pollen storm in the region, and deemed unrelated to study drug. Adverse events of grade 3–4 severity in the imatinib group related primarily to anticipated issues with shifts in liver function and blood cell counts. These events all resolved but required adjustments to study drug administration, as specified in the protocol. Of the 45 participants in the imatinib group, 20 (44%) had no modification in study drug administration, 17 (38%) had temporary modifications to dosing due to adverse events (seven for neutropaenia, four for rashes, two for abnormal liver function tests, and one each for gastrointestinal issues, thrombocytopaenia, cramps, and mental health concerns), and six (13%) were permanently discontinued due to adverse events (four for liver function abnormalities, one for pre-existing cardiac arrhythmia noted after randomisation, and one for persisting allergic skin rash). By contrast, 15 (68%) of 22 participants in the placebo group had no drug modification, five (23%) had transient adjustments due to adverse events (three for thrombocytopaenia, one for neutropaenia, and one for diabetic ketoacidosis), and none had a permanent discontinuation due to adverse events. In addition, although there were no indications to alter drug administration, one participant in each group temporarily discontinued imatinib or placebo and one participant in each group elected to permanently discontinue imatinib or placebo.

Seven participants had a total of 11 serious adverse events: four (89%) participants (eight events) in the imatinib group and three (14%) participants (three events) in the placebo group (appendix p 13). Two (4%) participants in the imatinib group each had three serious adverse events. Two of these events were considered possibly related to study drug (two skin infections in a single participant with a 2-month interval between the infections), and the remainder were considered to be unrelated to study drug.

Discussion

Given the challenges in managing type 1 diabetes, clinical trialists have sought drugs that can safely and effectively block autoimmune-mediated destruction of β cells, and have often tested immunotherapies targeting T cells. Transient effects have been observed with some of these drugs,[3–8] prompting the search for new approaches. Missing from the current armamentarium is a therapy that also affects metabolism, and improves β-cell health. Herein, we report, to our knowledge, the first trial of a tyrosine kinase inhibitor in recent-onset type 1 diabetes, utilising the first-in-class drug member imatinib. Although initially developed for use in chronic myeloid leukaemia, preclinical studies and clinical observations suggest that imatinib might offer a novel means to treat type 1 diabetes, via targeting of both immunological and metabolic pathways.[10,11,15–17,22] In designing the current trial, we sought to evaluate patient response while on therapy, and determine if there was a persisting effect after the course of imatinib, as was observed in NOD mouse studies after 10 weeks of imatinib exposure.[11] The imatinib group achieved the prespecified primary outcome, showing increased C-peptide AUC in response to MMTT at 12 months, compared with participants who received placebo. However, the effect was not sustained during a second year of observation off of therapy. Compared with the placebo group, imatinib-treated participants had lower exogenous insulin needs and had somewhat lower HbA_{1c} levels while on therapy, but these effects waned in the subsequent months off of therapy. These metabolic effects might stem from improved β-cell function and peripheral insulin sensitivity with imatinib.

Imatinib might act via a range of different mechanisms to alter the course of type 1 diabetes. Imatinib was first developed as a specific inhibitor of the ABL kinases to target the BCR-ABL fusion protein in chronic myeloid leukaemia. However, imatinib might also have broader clinical utility, as it also inhibits other tyrosine kinases, including PDGFR, KIT, CSF-1R, tyrosine-protein kinase ABL2, and tyrosine-protein kinase Lck.[9,15,17,22] In evaluation of the potential metabolic effects of imatinib, preclinical studies have reported effects on β-cells and on insulin sensitivity. Direct effects of imatinib on β-cell function include increased glucose-stimulated insulin secretion, and enhanced β-cell survival in the presence of various stressors, including a high-fat diet, cyclophosphamide, streptozotocin, and autoimmunity.[10,11,23] Han and colleagues reported reduced ER stress and increased β-beta cell mass in leptin-deficient (db/db) mice treated with imatinib.[14] Morita and colleagues expanded on these observations in the NOD mouse, noting that in the presence of ER stress, imatinib antagonises the interaction between ABL and the ER transmembrane kinase and endoribonuclease IRE1α, thereby blunting IRE1α hyperactivity, reducing β-cell apoptosis, and reversing diabetes.[12]

Several of our trial observations suggest that imatinib improved β-cell function during the course of the trial.

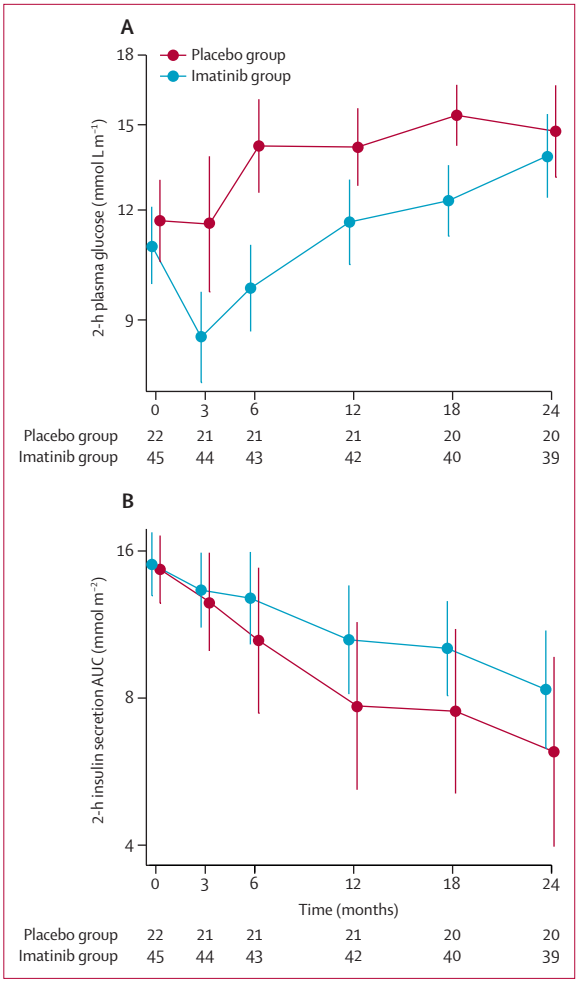

Figure 4: **MMTT responses**
2-h plasma glucose (A) and 2-h serum insulin secretion AUC (B) in response to MMTTs. Data are means and 95% CIs on a $\log_{10}$ scale. MMTT=mixed meal tolerance test. AUC=area under the curve.

β-cell glucose sensitivity improved during imatinib treatment, but diminished after the drug regimen was completed. The present analysis of β-cell glucose sensitivity has typically been used to evaluate β-cell function in type 2 diabetes, but has also been used to evaluate an at-risk type 1 diabetes population, and we have now applied this methodology to evaluate a post-diagnosis population.[24] Rather than simply analysing insulin secretion in response to an MMTT, β-cell glucose sensitivity provides a measure of the ability of the β cell to secrete insulin in response to a given glucose concentration, and might thus provide a better overall measure of β-cell function. If the effect of imatinib had been mediated solely by a change in insulin resistance, rather than also on β-cell function, then one would expect less insulin secreted for a given glucose level, rather than our observation of greater insulin secretion, as compared to findings in the placebo group; thus, the findings support an improvement in β-cell function. We also found that the proinsulin to C-peptide ratio was low

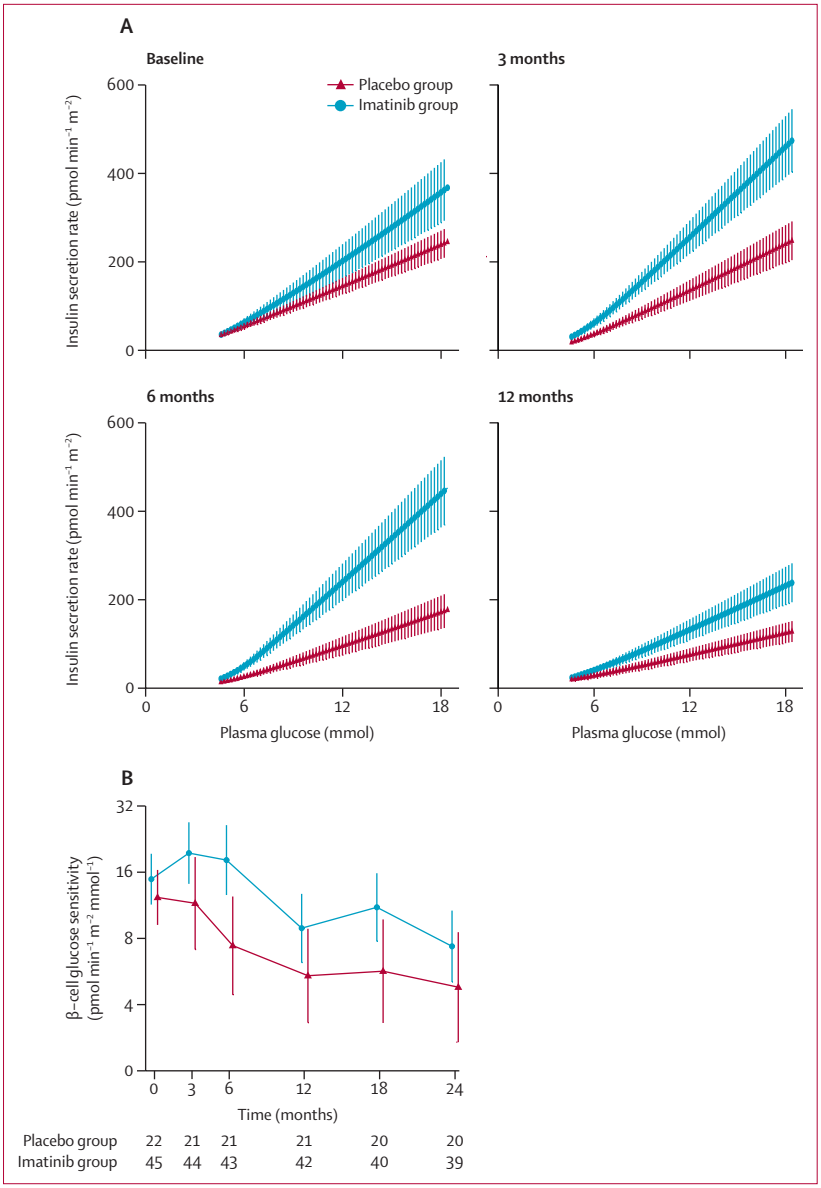

Figure 5: **β-cell glucose sensitivity**
A) Dose-response curves for insulin secretion rate versus plasma glucose concentration during the serial MMTTs. Data are the mean with SEM. The mean slope of the dose response is β-cell glucose sensitivity. B) β-cell glucose sensitivity presented as change in sensitivity with time on a $\log_{10}$ scale. Data are means with 95% CIs. n is number of patients with available data.

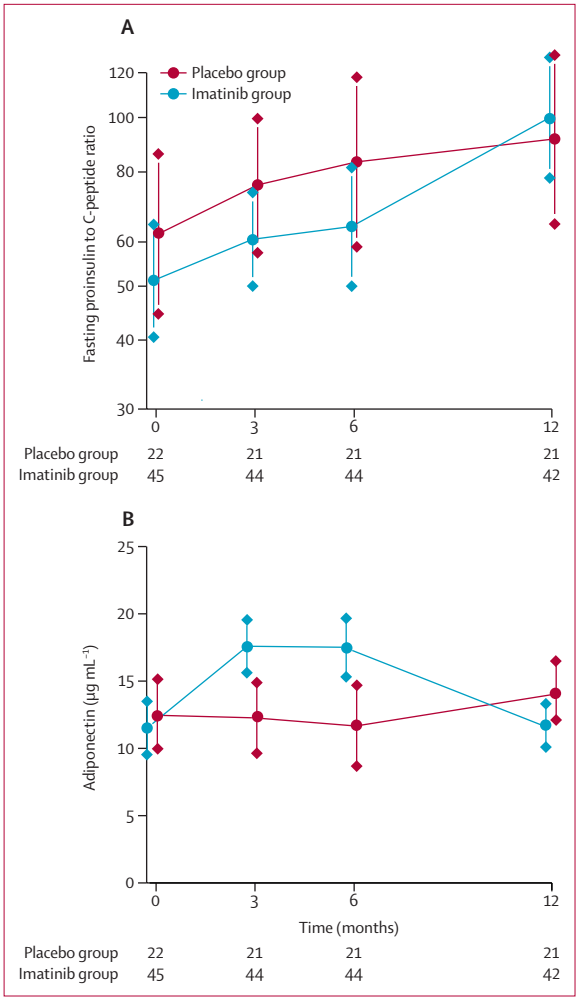

Figure 6: **Additional assessments of imatinib effects on β-cell function and metabolism.**
(A) Pro-insulin to C-peptide ratios with time. Data are means and 95% CIs on a non-linear scale under the transformation ln(pro-insulin ratio). (B) Serum adiponectin concentration with time. Data are means and 95% CIs.

during imatinib therapy, which has been linked with reduced ER stress and improved β-cell function.[25,26] Further evidence in support of an effect of imatinib on β-cell health is its effect on adiponectin concentrations: although an increase in adiponectin is often associated with improved insulin sensitivity, previous studies also suggest that adiponectin might decrease β-cell apoptosis and improve function via direct actions mediated by adiponectin receptors on β cells.[27] A final assay of interest in assessing the effect of imatinib on β-cell health was the β-cell death assay, in which we amplified the *INS* gene from participant sera by PCR. From our clinical samples, we did not see a difference between the imatinib and placebo groups with time. However, we note that the values measured were towards the lower limit of detection in the assay, and we might therefore have lacked the sensitivity to detect a difference in β-cell death.

Imatinib might also improve insulin sensitivity. In mice fed a high-fat diet, imatinib blocked PPARγ phosphorylation, which in turn improved insulin sensitivity and promoted browning of adipose tissue.[28] Imatinib has also been shown to improve insulin sensitivity in rats fed a high-fat diet, and induced remission of diabetes in db/db mice.[13,14] Several case reports and case series have noted that patients with type 2 diabetes have significant improvement or disease resolution (ie, improved glycemic control and lowering or discontinuation of antihyperglycaemic medications)

when treated with imatinib.[16] As noted previously[29] and in this study, imatinib therapy can increase serum adiponectin concentration, which has been associated with improvement in insulin sensitivity. No clinical studies to date have formally assessed changes in insulin sensitivity with imatinib; in our study, we noted a marked decrease in exogenous insulin needs while on therapy. We used glucose concentration and insulin secretion data from MMTTs to estimate insulin sensitivity with a validated method,[20] and found a marked difference between the imatinib and placebo groups at 6 months. Future formal testing with hyperglycaemic and euglycaemic clamp studies will help to clarify the effect of imatinib on insulin sensitivity.

Our interest in evaluating imatinib in this trial also stemmed from its possible immunological effects, and potential to block further autoimmune destruction of β cells, as suggested by preclinical studies, clinical reports, and small case series in various autoimmune conditions.[15,17,22] In past NOD mouse studies with imatinib, no significant changes were noted in various immunological mechanistic assays, including of T cell effector function and trafficking to islets, insulitis scores, $CD4^+$ cell to $CD8^+$ cell ratios in spleen and pancreatic lymph nodes, and regulatory T cell function.[11] Similarly, we found no immunological readout from peripheral blood samples that delineated imatinib-treated participants from placebo-treated participants, with no substantial changes in autoantibody titres with time, or changes in immune cell subsets by flow cytometry. These assessments of cell subsets are limited to immunophenotyping, which cannot detect potential effects on immunological function of the cells. Furthermore, our assessments were limited to sampling from the peripheral circulation, and thus we cannot determine if immunological changes might have occurred within the pancreatic lymph node or islets of participants treated with imatinib.

In planning this study, we were mindful of potential safety issues associated with imatinib, but anticipated that it might be better tolerated than in oncology settings, as we were working with relatively young adults with type 1 diabetes who were otherwise healthy. In general, imatinib was well tolerated, and when participants did develop adverse events, they tended to occur early in the course of imatinib administration, to be milder than described in the oncology literature,[30] and usually resolved in the ensuing days and weeks with ongoing therapy. We adopted a conservative algorithm for surveillance and modification of drug dosing for use in our study, enabling investigators to detect potential drug toxicities early in the treatment course. More than a third of imatinib-treated participants required a temporary modification in dosing, and six (13%) participants had to permanently discontinue imatinib. Thus, patients treated with imatinib should be carefully monitored, and the current algorithm can be used to guide drug administration in future studies.

	Imatinib (n=45)		Placebo (n=22)	
	Number of events	Number of participants*	Number of events	Number of participants*
Adverse event category				
Infections and infestations	26	12 (27%)	9	4 (18%)
Eye disorders	2	2 (4%)	0	0
Musculoskeletal and connective tissue disorders	4	3 (7%)	1	1 (5%)
CNS disorders	4	4 (9%)	0	0
Gastrointestinal disorders	13	6 (13%)	0	0
Metabolism and nutrition disorders	11	5 (11%)	2	2 (9%)
Reproductive system and breast disorders	1	1 (2%)†	0	0
Psychiatric disorders	9	5 (11%)	0	0
Respiratory, thoracic, and mediastinal disorders	6	6 (13%)	1	1 (5%)
Skin and subcutaneous tissue disorders	6	5 (11%)	3	2 (9%)
Ear and labyrinth disorders	1	1 (2%)	0	0
Cardiac disorders	6	4 (9%)	0	0
General disorders or administration site conditions	2	2 (4%)	0	0
Laboratory investigations	18	10 (22%)	4	2 (9%)
Pregnancy, puerperium, and perinatal conditions	0	0	1	1 (5%)
Injury, poisoning, and procedural complications	4	2 (4%)	0	0
Immune system disorders	0	0	1	1 (5%)
Hepatobiliary disorders	5	3 (7%)	2	2 (9%)
Surgical and medical procedures	0	0	2	2 (9%)
Blood and lymphatic system disorders	7	4 (9%)	0	0
Endocrine disorders	45	4 (9%)	2	1 (5%)
Renal and urinary disorders	2	1 (2%)	0	0
Totals	172	32 (71%)	28	13 (59%)

Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. *Some participants had more than one adverse event of grade 2 severity or worse. †The only grade 5 event (death) due to acute asthma exacerbation; deemed unrelated to study drug.

Table 2: **Adverse events of grade 2 severity or worse**

Limitations of this study include the modest sample size; confinement to adults and inclusion almost exclusively of white individuals; and association with possible safety issues, with the more frequent dose adjustments and side-effect profile for those on imatinib possibly weakening the blinding of study group assignment. Furthermore, the study evaluated the effect of only a 6-month treatment period. Nonetheless, compared with results from successful phase 2 trials in recent-onset type 1 diabetes, the 19·4% effect size we found with imatinib at 12 months compares favourably with several other drugs, including rituximab, alefacept, and abatacept.[31] Thus, further evaluation of the use of imatinib in type 1 diabetes might be warranted. Although imatinib is approved for use in children with chronic myeloid leukaemia aged 3 years and older, we were limited in this study to an adult population, so as to clarify potential safety issues and document a prospect of benefit in this population. The rate of β-cell loss occurs slower in adults than in children, and some fundamental differences in the disease process might be associated with age of type 1 diabetes presentation.[32] As suggested with other drugs, including CTLA4-Ig, anti-CD20, and anti-CD3 monoclonal

antibodies,[3,4,7] imatinib might prove to be more efficacious in children with recent-onset type 1 diabetes than in adults. The ideal dose and duration of imatinib therapy requires further evaluation. We used a standard starting dose employed in oncology, but benefits in type 1 diabetes might occur at lower doses, and with reduced risk of adverse effects. Unlike in the NOD mouse, the metabolic benefits in treated participants were not sustained when imatinib was withdrawn, and thus continuous or chronic intermittent therapy might be required. An additional question is whether imatinib will offer an additive or synergistic response when used in combination with a drug that works by an alternative mechanism, such as teplizumab or anti-thymocyte globulin, which have immunomodulatory effects on T cells. Imatinib might also prove more efficacious if used earlier in the course of disease, such as at stage 2, when β-cell function is decreasing, but before more overt hyperglycaemia at stage 3.[33] The list of approved tyrosine kinase inhibitors with varied specificities continues to increase steadily, and as more is learnt about the most crucial pathways to target in type 1 diabetes, a better drug might be identified in this class to consider for the treatment of type 1 diabetes.

In summary, this phase 2 study showed that 26 weeks of treatment with imatinib slowed the decrease in β-cell function for up to 12 months, although this effect was not sustained out to 24 months. Imatinib treatment might have novel effects on metabolism leading to improved β-cell function and insulin sensitivity. These initial observations suggest considerations for future study of imatinib in type 1 diabetes, provided treated participants are closely monitored for possible toxicities.

Contributors

SEG served as study chair, and wrote the first draft of the manuscript. Other members of the writing group included the listed authors. All authors were involved in the conduct of the trial, and the collection and review of study data. SEG, BNB, and JPK accessed and verified the data. The writing group had full access to all of the data and made the decision to submit for publication. All authors reviewed and commented on various versions of the paper and the suggested revisions.

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Declaration of interests

SEG has served on advisory boards for Avotres, Provention Bio, and Tolerion, and participated in clinical trials with Caladrius, Intrexon, Janssen, Provention Bio, and Tolerion. JLG has consulted for Vertex Pharmaceuticals and Regeneron Pharmaceuticals, and participated in clinical trials for Avotres, Caladrius, Janssen, and Tolerion. PAG has served on advisory boards for Caladrius, Bristol Myers Squibb, and Lilly, received grant support from Caladrius, Novo Nordisk, and Pfizer, and is co-founder and chief medical officer for ImmunoMolecular Therapeutics. RGM has a patent application for DNA methylation in inflammatory disease. SMW reports serving on advisory boards for Boehringer Ingelheim Pharmaceuticals and Medtronic, and a data and safety monitoring board for the US National Institutes of Health (NIH). All other authors declare no competing interests.

Data sharing

Data collected for the study and presented herein will be made available to others. Data will be organised in a data dictionary, and participant data will be de-identified. Related study documents, including the study protocol, informed consent forms, and statistical analysis plan, will also be available. Data requests should be sent by email to the corresponding author (stephen.gitelman@ucsf.edu), who will partner with the coordinating centre at the University of South Florida to supply the requested information via disk.

Acknowledgments

The trial was sponsored by the Juvenile Diabetes Research Foundation. The collection and storage of samples for mechanistic assays reported in this publication were also supported by the Immune Tolerance Network, which is supported by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Allergy and Infectious Diseases of the NIH under award number UM1AI109565. Members of the DSMB are listed in the appendix (p 15). We thank Peter Sayre and Elisavet Serti from the Immune Tolerance Network for their contributions as study medical monitor and in overseeing mechanistic studies, respectively, and Sheila Scheiding from the Human Immunophenotyping Core Laboratory at Benaroya Research Institute for her assistance with mechanistic study analyses. The project was supported in part by NIH Clinical and Translational Award grants from the National Center for Research Resources (grant numbers UL1TR000004 [to University of California San Francisco]), UL1TR002537 [to University of Iowa]), 1UL1TR001108 [to Indiana University School of Medicine], UL1TR001878 [to the Children's Hospital of Philadelphia and University of Pennsylvania], and P30DK036836 [to the Joslin Diabetes Center]). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Novartis (Cambridge, MA, USA) supplied study drug and matching placebo, and gave input regarding dosage and safety, but had no direct involvement with study design, conduct, or management; data collection, analysis, or interpretation; or manuscript preparation. There are no agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named.

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