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Study Design (Part 3 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)

In 1 collection

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ABSTRACT

This is Part 3 of "Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-Onset Type 1 Diabetes Mellitus".

This clinical study is supported by JDRF. The aim of the collection is to determine whether imatinib will slow the progression of the autoimmune destruction of ß cells and lead to the preservation of C-peptide secretion in T1DM and to assess Diabetes-related objectives and safety of Imatinib in new-onset type 1 diabetes mellitus".

ATTACHMENTS

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COLLECTIONS

Collection of Protocols and Guidelines for Safety and Efficacy of Imatinib for Preserving Beta-cell Function in New-onset Type 1 Diabetes Mellitus

KEYWORDS

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Collection of Protocols and Guidelines for Safety and Efficacy of Imatinib for Preserving Beta-cell Function in New-onset Type 1 Diabetes Mellitus

GUIDELINES

3.1 DESCRIPTION

The study will be a multicenter, two-arm, double-blind, placebo-controlled, 2:1 randomly assigned, phase II clinical trial for individuals with recent-onset T1DM. The randomly assigned participants will receive either a 6-month course of imatinib or matching placebo tablets over a period of 26 weeks. Both treatment and placebo groups will undergo identical procedures and will be followed for 104 weeks. The primary endpoint, 2-hour C-peptide AUC measured at 52 weeks in response to a mixed-meal tolerance test (MMTT), will be measured at 52 weeks. Safety, diabetes control, ß-cell function, and immune function will be assessed for 104 weeks. Both groups will receive intensive diabetes management. During the follow-up phase, participants will undergo serial clinical and immunologic assessments over the 104 week study period, and possible mechanisms of imatinib action will be assessed.

Initial enrollment will be for subjects ages 18-45, with the goal to lower the age down to 12 upon acceptable safety review and prospect of benefit for this initial older cohort. When the first 10 enrollees have completed their week 26 assessment, the safety data will be reviewed by a subcommittee that includes the protocol chairs, the medical monitor, the clinical trial physician, and the DSMB. If the review concludes that significant safety concerns have been identified, then no further enrollment will occur pending further data review and evaluation by the DSMB. If the DSMB decides that the study may proceed then the FDA will be notified of study progress and determine if further age restriction is necessary, or if enrollment may be opened for subjects down to age 12. After the first 21 subjects have completed 6 months, a further safety review will occur for the DSMB. Additionally, an interim efficacy assessment will be conducted for the DSMB and FDA. The FDA will again be apprised of study progress, with further consideration for lowering the age of enrollees to 12, if this has not occurred earlier. If and when the age is lowered, an identical review procedure will be followed when the first 10 pediatric participants (ages 12-17) have completed their week 26 assessment. If the review is satisfactory, then enrollment will continue for subjects ages 12-45 until the study is fully enrolled.

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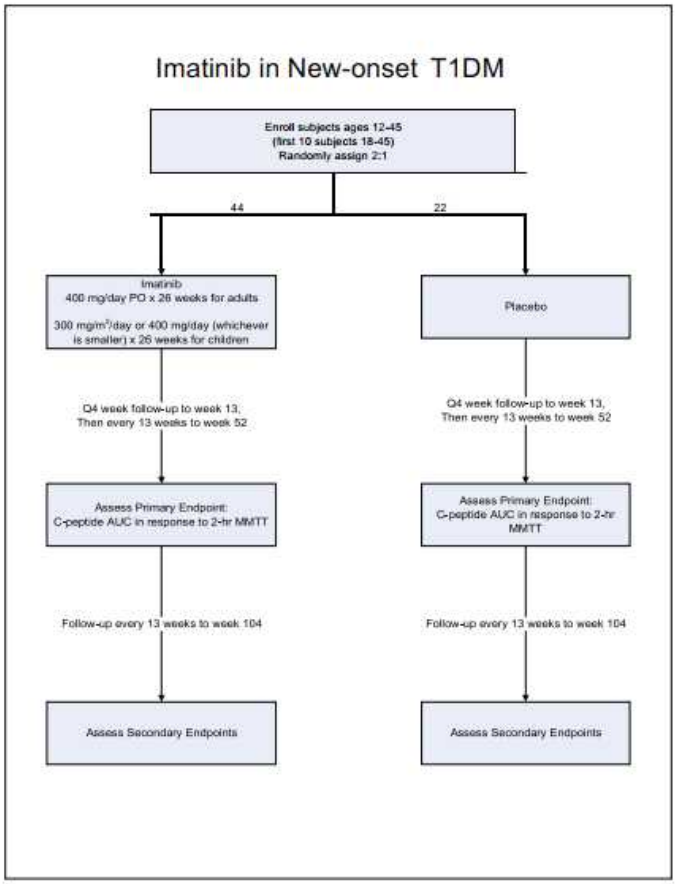

Figure 3. Study Schema

3.2 STUDY DURATION AND PACE OF ENROLLMENT

Total study duration is expected to be approximately 4 years. Recruitment is anticipated to be completed in 18 to 24 months. Individual study participation is 24 months.

3.3 STUDY ENDPOINTS

3.3.1 Primary Endpoint

The primary endpoint is an MMTT-stimulated 2 hour C-peptide AUC at week 52.

3.3.2 Secondary Endpoints

Efficacy:

1. MMTT-stimulated peak and 4 hour C-peptide AUC at weeks 52 and 104.
2. MMTT-stimulated 2 hour C-peptide AUC at week 104.
3. MMTT-stimulated 2-hour C-peptide AUC assessed longitudinally at weeks -2, 13, 26, 52, 78, and 104.
4. Insulin use in units per kilogram body weight per day at weeks 52 and 104.
5. Major hypoglycemic events, as defined in section 8.2.1, occurring from randomization at weeks 0, 52 and 104.
6. HbA1c levels at weeks 52 and 104.

Safety:

The rate of the following AEs in participants receiving imatinib or placebo:

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1. Myelosuppression.
2. Gastrointestinal disorders.
3. Infections.
4. Hepatotoxicity.
5. Cardiac toxicity and edema.
6. Cutaneous reactions.
7. Muscle cramps, bone pain, arthralgias.
8. Fluid retention or peripheral edema.
9. Bone metabolism and growth abnormalities
10. Frequency and severity of all AEs in participants receiving imatinib or placebo.

3.3.3 Exploratory Endpoints

Mechanistic:

Immunological assessments described in section 7 will be compared with clinical outcomes to determine whether there is evidence of immune tolerance to diabetes associated autoantigens.

Metabolic (see section 6.1.1 for further discussion):

1. Proportion of patients who are exogenous insulin-free (for at least 3 months) with an HbA1C ≤ 6.5% at weeks 52 and 104 in each treatment arm.
2. Proportion of subjects who achieve a persistent reduction (for at least 3 months) in insulin dose to < 0.5 units/kg at weeks 52 and 104 in each treatment arm.
3. Effects on insulin resistance will be evaluated using modeling from data obtained on MMTTs, and by assessing change in adiponectin, proinsulin levels (and proinsulin/c-peptide ratio), and glucagon.

3.4 RATIONALE FOR CLINICAL TRIAL DESIGN

The proposed trial will evaluate imatinib, a tyrosine kinase inhibitor, as a novel tolerance-inducing intervention in new-onset T1DM. As with ITN and TrialNet newonset T1DM studies, endogenous insulin secretion will be assessed serially by measuring C-peptide AUC in response to a 4-hour MMTT. The proposed primary endpoint is a 2-hour C-peptide AUC in response to MMTT at week 52. This endpoint is in accord with an ADA workshop,[173] and the TrialNet consensus guidelines for newonset T1DM studies. Other clinical outcome measures of efficacy include insulin use, HbA1C, and major hypoglycemic events. The safety of patients in this study will be closely monitored, and expected adverse events related to imatinib have been selected as the secondary endpoints for safety (see section 3.3.2).

In accord with other ITN and TrialNet new-onset T1DM studies, we plan to randomly assign participants 2:1 (treatment vs. placebo). The greater chance of enrolling into a drug treatment arm has helped facilitate recruitment for such trials. Participants between ages 12 and 45 years will be recruited. T1DM can occur at any age, but it occurs with dramatically increased incidence in children. The average age of children at presentation of this disease is approximately 13 years, and most individuals present when they are under the age of 18 years. The incidence of T1DM is increasing at approximately 3% per year, mainly in the younger population.[165] Beta cell function declines faster in those < 21 years of age, relative to those > age 21 (Greenbaum et al, Diabetes) [178]. Many new-onset T1DM studies enroll up to age 45; the upper age limit is restricted in this study to45 so that the trial will enrich for a group of subjects who are more likely to have a faster rate of decline in beta cell function, and therefore enable a more pronounced difference between those in the treatment versus placebo group, assuming the therapy will have an effect. Imatinib is approved for the treatment of chronic myeloid leukemia in children down to age 3 years. The dosing is adjusted for body surface area, and the safety spectrum appears to be comparable to that in adults. Additional justification for the inclusion of children is presented in section 1.5.2.

We will treat participants within 100 days of their T1DM diagnosis. Past studies have suggested that subjects respond better with this earlier enrollment ,[29,36] and currently all recent-onset T1DM immunotherapy trials conducted by TrialNet , ITN, and many pharmaceutical studies enroll patients within 100 days of diagnosis[36,38]. We have elected to have a 52-week primary endpoint for this trial, again in accord with ITN and TrialNet new-onset studies. It is important to consider whether the degree of C-peptide decline in the placebo group with optimal

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diabetes management is significant enough during the first year of diagnosis to detect a difference between the imatinib group and the placebo group. Steele et al. demonstrated that those with new-onset T1DM have steady, progressive loss in ß-cell function from the time of diagnosis, as assessed by C-peptide AUC in response to an MMTT, the measure to be employed in this study.[9] This finding has been corroborated by others in a series of new onset T1DM trials.[27,34,36-39,174,175]

The metabolic and immunological / tolerogenic effect of imatinib will continue to be assessed during the follow-up phase (months 12–24). Preservation of C-peptide levels at the end of the follow-up phase in the imatinib group will be an indication of whether imatinib induces tolerance. A host of immunologic assays performed throughout the study will also provide insight into the mechanism of imatinib action and its possible tolerogenic properties (Refer to section 7 for a complete discussion of immunologic assays.)

3.5 RATIONALE FOR SELECTION OF DRUG, ROUTE, DOSE, AND REGIMEN

There have been a series of studies to define dose-response relationships with imatinib, beginning with the early phase 1 studies in CML.[46,47,176] Doses between 200 to 300 mg/day appear to be on the steep part of the dose response curve. A dose that achieves concentrations of 1 µmol/L, which inhibits Bcr-Abl kinase activity, appears to be optimal for inducing apoptosis, and these are the trough levels achieved in phase I studies of subjects on 260 mg/day. Thus, 260 mg has been considered a threshold dose for inducing optimal therapeutic responses. To ensure that the majority of treated subjects were above this threshold, 400 mg/day was adopted as the dose for phase II studies of patients with chronic disease, and with a half-life of 13–16 hours, once daily dosing was considered adequate. This dosing regimen has proven to be highly successful in treating CML and GIST.[44-48] Doses higher than 400 mg/day may achieve better responses, particularly for those in accelerated and blast crisis studies. Doses of up to 1000 mg have been reached without convincing dose-limiting toxicity but, as noted above, the frequency and grade of adverse events increases, particularly above 600 mg/day.

The responses in autoimmunity noted above were achieved in subjects receiving at least 400 mg/day, and sometimes higher imatinib doses. Thus, 400 mg/day appears to be an effective dose in autoimmune diseases.

It is difficult to extrapolate exactly from the mouse dose employed by Louvet et al[112] to humans. They were successful with doses of 50 mg and 100 mg/kg and 1.5 to 3 mg/mouse, and ultimately used 1.5 mg/mouse. Druker considers this dose roughly comparable to 400 mg/day used in clinical studies (personal communication).

A common question with all studies is whether or not dose should be adjusted for a participant's size. Peng et al conducted a study to determine whether obesity had an effect on plasma levels of imatinib, and concluded that there was no evidence that patient size needed to be taken into consideration.[177] Deininger et al also reported that flat dosing was appropriate in a small number of obese subjects.[129] Considerations for children were reviewed in section 1.5.2, and we will follow the standard dosing of 260 mg/m2 or 400 mg, whichever is lower, stated in the Gleevec package insert.

One additional consideration with regard to dosing is how long to continue drug therapy. Longer-term treatment (10 weeks versus 3 weeks) clearly resulted in a more robust and durable response in the NOD mouse. Based on this, we propose a 6-month treatment period—6 months strikes the appropriate balance between too short a period, with loss of long-term efficacy, and longer treatment (such as 12 months) with ongoing risk from the therapy. For its approved indications, Gleevec therapy is typically administered for years and even lifelong in some patients, but in this trial we will be assessing its role as a tolerizing agent after 6 months of therapy.

3.6 MEASURES TO MINIMIZE BIAS

The proposed trial has a double-blind design. One salient issue is whether or not the side effect profile will be such that it will serve to unmask a significant number of participants and study personnel. We expect that the side effects will be milder and less frequent than seen in oncology settings, as we will be enrolling a younger and healthier patient population who will be treated at the lowest therapeutic imatinib dose (B. Druker, personal communication). Both the treatment and placebo groups will require close, regular monitoring, particularly during the treatment phase. Because endogenous insulin secretion is the primary outcome variable (i.e., C-peptide), and this in turn is affected by glycemic control, we will aim for comparable glycemic control in both groups, treating to established targets. The health care professionals managing T1DM will be blinded to treatment assignment.

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3.7 STOPPING RULES

3.7.1 Ongoing Review

The progress of the study will be monitored by a Data and Safety Monitoring Board (DSMB), which will review safety data and make recommendations regarding continuation, termination, or modification of the study. Based on an 18- to 24-month recruitment period and an additional study period of 24 months, the DSMB will formally review the safety data at least yearly. The number of subjects who discontinue study treatment will also be included in the reports prepared for the DSMB.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the medical monitor, clinical trial physician, or protocol chairs to warrant review, or when an event occurs that contributes to a stopping rule listed in Section 5.3.

3.7.2 Stopping Rule Guidance

3.7.2.1 Study-related adverse events

If any of the following events occur, enrollment will be suspended and the DSMB chair will be notified such that a review of safety data will be conducted to determine if enrollment in the study will be stopped and/or administration of investigational study medication should be halted:
• Any death except those assessed as not related to study treatment on review by the protocol chairs, the clinical trial physician, and the medical monitor.
• One or more participants experience treatment-emergent, clinically significant cardiac toxicity.
• Two or more of the first 10 treated participants or ≥20% of all treated participants experience a clinically significant, drug-related adverse event resulting in the permanent discontinuation of study treatment, as defined in section 5.3.
• If two or more of the first 10 treated growing-age participants, as defined in section 5.2.9, or greater than 20% of all treated growing-age participants, exhibit a decrease in Height Standard Deviation Score (Ht-SDS) of > 0.5 from baseline at 6 months, or > 0.8 from baseline at 12 months, then enrollment will pause for growing-age participants. Study enrollment will continue for participants who are not growingage. DSMB review will determine whether imatinib treatment can resume in growing-age participants based on available growth and bone-metabolism data, as well as bone-age radiographs.

REFERENCES

9. Steele C, Hagopian WA, Gitelman S, et al. Insulin secretion in type 1 diabetes. Diabetes. Feb 2004;53(2):426-433.
27. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. Nov 2009;361(22):2143-2152.
29. Group TC-ERCT. Cyclosporin-induced remission of IDDM after early intervention. Association of 1 yr of cyclosporin treatment with enhanced insulin secretion. Diabetes. Nov 1988;37(11):1574-1582.
34. Herold KC, Gitelman SE, Masharani U, et al. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. Diabetes. Jun 2005;54(6):1763- 1769.
36. Sherry N, Hagopian W, Ludvigsson J, et al. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. Lancet. Aug 2011;378(9790):487-497.
37. Wherrett DK, Bundy B, Becker DJ, et al. Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial. Lancet. Jul 2011;378(9788):319-327.
38. Ludviggson J, Krisky D, Casas R, et al. GAD65 Antigen Therapy in Recently Diagnosed Type 1 Diabetes Mellitus. NEJM. 2012.
39. Orban T, Bundy B, Becker DJ, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet. Jul 2011;378(9789):412-419.
44. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood. Apr 1 2005;105(7):2640-2653.
45. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. Dec 7 2006;355(23):2408-2417.

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46. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med. Apr 5 2001;344(14):1038-1042.
47. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCRABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. Apr 5 2001;344(14):1031- 1037.
48. Kantarjian HM, Cortes JE, O'Brien S, et al. Long-term survival benefit and improved complete cytogenetic and molecular response rates with imatinib mesylate in Philadelphia chromosomepositive chronic-phase chronic myeloid leukemia after failure of interferon-alpha. Blood. Oct 1 2004;104(7):1979-1988.
112. Louvet C, Szot GL, Lang J, et al. Tyrosine kinase inhibitors reverse type 1 diabetes in nonobese diabetic mice. Proc Natl Acad Sci U S A. Dec 2 2008;105(48):18895-18900.
129. Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. J Clin Oncol. Apr 15 2003;21(8):1637-1647.
165. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. Jun 13 2009;373(9680):2027-2033.
173. Palmer JP, Fleming GA, Greenbaum CJ, et al. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. Diabetes. Jan 2004;53(1):250-264.
174. Ludvigsson J, Faresjo M, Hjorth M, et al. GAD treatment and insulin secretion in recent-onset type 1 diabetes. N Engl J Med. Oct 30 2008;359(18):1909-1920.
175. Gottlieb PA, Quinlan S, Krause-Steinrauf H, et al. Failure to preserve beta-cell function with mycophenolate mofetil and daclizumab combined therapy in patients with new- onset type 1 diabetes. Diabetes Care. Apr 2010;33(4):826-832.
176. Braziel RM, Launder TM, Druker BJ, et al. Hematopathologic and cytogenetic findings in imatinib mesylate-treated chronic myelogenous leukemia patients: 14 months' experience. Blood. Jul 15 2002;100(2):435-441.
177. Peng B, Hayes M, Resta D, et al. Pharmacokinetics and pharmacodynamics of imatinib in a phase I trial with chronic myeloid leukemia patients. J Clin Oncol. Mar 1 2004;22(5):935-942.
178. Greenbaum CJ, Beam CA, Coulware D, Gitelman SE, Gottlieb PA, Herold KC, Lachin JM, McGee P, Palmer JP, Pescovitz MD, Krause-Steinrauf H, Skyler JS, Sosenko JM, Type 1 Diabetes TrialNet Study Group. Fall in C-peptide Over First Two Years from Diagnosis: Evidence of At Least Two Distinct Phases from Composite TrialNet Data. Diabetes. 2012; 61: 2066-2073.

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