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Study Medications (Part 5 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 5 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

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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

5.1 INVESTIGATIONAL MEDICATION

5.1.1 Formulation and Packaging

Imatinib mesylate (Gleevec; Novartis, East Hanover, NJ) is produced as film-coated tablets, equivalent to 100 mg of imatinib free base. The placebo group will receive an identical pill that is manufactured and distributed by a designated drug distributor. If necessary to prevent unblinding, the distributor may need to overencapsulate the imatinib tablets.

5.1.2 Dosage, Preparation, and Administration

Adult participants will receive four 100 mg tablets of imatinib or the corresponding placebo tablets daily for the first 6 months. Pediatric participants will receive 260 mg/m2/day (rounded up or to the closest 100 mg) or 400 mg/day (whichever is smaller) of active drug or placebo.

5.1.3 Recommended Storage Conditions

- Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).
- Protect from moisture.
- Dispense in a tight container, USP.

5.2 DOSE MODIFICATION AND MANAGEMENT OF ADVERSE EVENTS

With the use of a relatively low dose of imatinib in an otherwise healthy population, we hope to minimize the nature and extent of AEs experienced. It is important to note here, as in section 1.4, that the AEs referenced below, if observed, will usually occur early in the course of treatment, are often self-limited, and do not usually require dose adjustment or discontinuation of imatinib. Nonetheless, the investigative team recognizes that cancer treatment is clearly different than the proposed elective clinical trial: side effects considered acceptable and tolerable in a cancer setting may not be considered in the same light for subjects in this study. Every effort will be made to carefully balance the intent to provide the maximum total prescribed dose of study drug to subjects, versus the discomfort and risk that may be accompanied with imatinib administration. The “art” of subject management in this study will be to minimize the number of subjects that drop out of the trial due to these side effects, working in close concert with the investigative team to either adjust study drug dose and/or provide symptomatic relief with concomitant medications. General guidelines are outlined below, but may need to be modified as deemed necessary, in consultation with the trial physicians and medical monitor. In general, when a dose reduction is required, the daily dose of imatinib or placebo will be halved: For adults, the dose will be reduced from 400 mg/day to 200 mg/day. Unless otherwise stated, the equivalent dose reduction in children will be from 260 mg/m^2/day to 130 mg/m^2/day. Investigators will be instructed to always round up to the nearest 50 mg increment for the half-dose dosage.

5.2.1 Gastrointestinal Reactions

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Nausea. To minimize issues with nausea, participants will be advised to take study medication with the largest meal of the day. If the problem persists, they may need to split the study medication into twice daily dosing.

For recurrent, persistent vomiting, grades 1 and 2, lasting for 48 hours, investigators will consider the use of anti-emetics such as prochloropherazine or ondansetron. Subjects usually respond promptly, and dose reduction is seldom needed.

For grade 2 vomiting that persists for 48 hours despite the use of antiemetic drugs, imatinib will be reduced to 50% of the initial daily dose. If vomiting resolves over the ensuing week, then the full dose will be restored. If vomiting recurs, then the subject will need to remain on the 50% tolerated lower dose, and re-evaluated weekly, with return to full dose reconsidered.

For vomiting that is grade 3, or grade 2 that does not improve with anti-emetics and dose reduction for 48 hours,, imatinib will be suspended until the problem is resolved. Electrolytes should be obtained. Imatinib will then be reintroduced at 50% of the initial daily dose. If vomiting does not recur over the ensuing week, the initial dose will be restored. If vomiting of grade 3 recurs, then the drug will be permanently discontinued. If nausea or vomiting resolve and then occur again at a later time, the same procedures may be followed as outlined above, depending on the grade.

Diarrhea. If it occurs, diarrhea is often mild and requires no specific therapy. For persistent diarrhea (1 week or greater) of grades 1 and 2 the participant may be treated with antidiarrheal and antispasmotic drugs, such as Imodium®, Lomotil®, or paregoric, at the discretion of the investigator.

For grade 2 diarrhea that persists for 1 week despite the use of antidiarrheal drugs, imatinib will be reduced to 50% of the initial dose. If diarrhea improves to less than or equal to grade 1 for at least 1 week, the initial dose will be restored. If diarrhea persists despite use of antidiarrheal drugs and dose reduction, permanent discontinuation of imatinib will be considered.

For diarrhea of grade 3 or higher, imatinib will be suspended until the problem is resolved. Electrolytes should be obtained. Imatinib will then be reintroduced at 50% of the initial dose for 1 week. If diarrhea does not recur, the initial dose will be restored. If diarrhea greater than grade 2 recurs, imatinib will be permanently discontinued. If diarrhea resolves and then occurs again at a later time, the same procedure may be followed.

Chronic diarrhea, of 14 or more days in duration, should be evaluated to determine if there is an infectious cause. Evaluation will be conducted in consultation with local infectious disease consultants, and will include a thorough clinical and epidemiological evaluation, including travel history and any possible exposures. Stool culture and other evaluation may be required, and anti-microbial therapy offered as indicated. Other potential causes of diarrhea, such as lactase deficiency, should be considered.

5.2.2 Muscle Cramps, Bone Pain, Arthralgias

Mild to moderate cramps may respond to calcium and magnesium supplementation, and some have responded to quinine. Mild to moderate bone pain and arthralgia can usually be relieved with nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen.

For grade 2 muscle cramps, bone pain or arthralgia that persist for 1 week despite the use of symptom-relieving drugs, the dose of imatinib will be reduced to 50% of the initial daily dose. If symptoms improve to less than or equal to grade 1 for at least 1 week, the initial dose will be restored. If symptoms persist despite symptomatic treatment and dose reduction, permanent discontinuation of imatinib will be considered.

For grade 3 muscle cramps, bone pain or arthralgia, imatinib will be suspended until the problem is resolved. Imatinib will then be reintroduced at 50% of the initial dose for 1 week. If symptoms do not recur, the initial dose will be restored. If symptoms greater than grade 2 recur, imatinib will be permanently discontinued.

5.2.3 Edema

Edema associated with imatinib is usually mild and self-limited, and often does not require therapy. Affected participants may consider a reduction in salt intake. Patients with periorbital edema may benefit from topical

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0.25% phenylephrine or 1% hydrocortisone.

Localized edema. Grade 2 localized edema, including periorbital edema and limb edema, that persists for longer than 1 week may be treated with diuretics. For grade 2 edema that persists despite the measures described above, the dose of imatinib will be reduced to 50% of the initial daily dose. If edema improves to less than or equal to grade 1 for at least 1 week, the initial dose will be restored. If edema persists despite reductions in salt intake, use of diuretics, and imatinib dose reduction, permanent discontinuation of imatinib will be considered.

For edema of grade 3 or higher, imatinib will be suspended until the problem is resolved. Imatinib will then be reintroduced, with ongoing diuretic use, at 50% of the initial daily dose for 1 week. If edema does not recur, the initial dose will be restored. If edema greater than grade 2 recurs, imatinib will be permanently discontinued. If localized edema resolves and then occurs again at a later time, the same procedure may be followed.

Generalized fluid retention. Participants will be monitored for signs and symptoms of generalized fluid retention (including pulmonary and cardiac issues), and will be weighed regularly at each study visit to detect the early onset of fluid retention. If sudden increases in weight occur, participants should be examined for signs of pulmonary edema, pleural effusion, pericardial effusion, and ascites. If any signs of generalized fluid retention are found, imatinib should be suspended and diuretic therapy started. Electrolytes should also be obtained if greater than grade 2. If these measures lead to a prompt resolution of fluid retention, imatinib may be reintroduced at 50% of the initial daily dose. If fluid retention does not recur, the initial dose may be restored. If generalized fluid retention recurs, imatinib will be permanently discontinued.

5.2.4 Cutaneous Reactions

Rash. Investigators should be prepared for rashes early in the course of therapy, when they are most likely to occur. These are usually grades 1 or 2 and are self-limited. Symptomatic treatment with antihistamines, salves, and coal tar preparations has been helpful.

For grade 2 rash that persists for 1 week despite the measures described above, the dose of imatinib will be reduced to 50% of the initial daily dose. If the rash improves to less than or equal to grade 1 for at least 1 week, the initial dose will be restored. If the grade 2 rash persists despite symptomatic treatment and imatinib dose reduction, permanent discontinuation of imatinib will be considered. If grade 2 rash resolves and then occurs again at a later time, the same procedure may be followed.

For a rash of grade 3 or higher, imatinib will be suspended until the problem is resolved. Imatinib will then be reintroduced at 50% of the initial dose for 1 week. If the rash does not recur, the initial dose will be restored. If a rash greater than grade 2 recurs, imatinib will be permanently discontinued.

Bullous dermatologic reactions. Rare cases of bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with imatinib treatment.

In cases of less than or equal to grade 1 erythema multiforme, imatinib will be suspended. If the condition resolves promptly, reintroduction of imatinib may be considered, starting at the lowest dose (100 mg/day) with gradual dose escalation, if tolerated. If the condition recurs at any grade, imatinib will be permanently discontinued.

If a participant presents with Stevens-Johnson syndrome (any grade), toxic epidermal necrolysis (any grade), or > grade 1 erythema multiforme, imatinib will be permanently discontinued and supportive therapy, including systemic glucocorticoids, started immediately.

5.2.5 Hepatotoxicity

In general, guidelines established for imatinib use in CML and GIST will be followed, 129,130 but a more conservative approach will be used, as follows. Liver function tests (LFTs) will be obtained every other week during the first month of therapy, and monthly thereafter.

For grade-2 transaminase (ALT or AST > 3.0 ´ ULN) or bilirubin (> 1.5 ´ ULN) elevations, imatinib must be suspended, and the LFTs monitored weekly. When they have fallen to grade 1 or normalized, imatinib will be restarted at 50% of the initial daily dose. If the liver toxicity does not recur within 6–12 weeks, then the initial dose

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will be restored. If after resumption of treatment grade 2 transaminase or bilirubin elevations recur, study drug will be permanently discontinued.

For grade-1 abnormalities (ALT or AST greater than or equal to 1.0–3.0 ´ ULN; bilirubin greater than or equal to1.0-1.5 ´ ULN), imatinib treatment can be continued but LFTs will be monitored weekly for 2 weeks and then, if no worsening is observed, every other week. Concomitant hepatotoxic agents, such as alcohol or acetaminophen, should be removed. Persisting grade 1 abnormalities should be managed by dose reduction, biweekly monitoring, and further evaluation in conjunction with gastroenterology consultation.

5.2.6 Myelosuppression

In general, recommendations will be a conservative algorithm, derived from Deininger et al. for the chronic phase of CML will be followed.[129] For grade 1 neutropenia (absolute neutrophil count [ANC] <LLN-1500/mm^3) and thrombocytopenia (<LLN- 75,000/ mm^3), the dose of imatinib will be reduced to 50% of the initial dose. Counts will be monitored bi-weekly. The initial dose will be restored when myelosuppression resolves.

For grade 2 or greater events (ANC less than 1,500/mm^3, or platelets less than 50,000/mm^3) imatinib should be suspended and the counts will be repeated weekly until they have recovered (ANC greater than 1,500/mm^3, platelets greater than 75,000/mm^3). For grade 1 neutrophil or platelet levels, imatinib will be restarted at 50% of the original dose, and the counts will be monitored biweekly; imatinib will be restored to the full dose when the counts normalize. If myelosuppression resolves and then occurs again at a later time, the same procedure may be followed.

5.2.7 Infectious Disease Risk

In general, higher risk for infections has not been a concern during the clinical use of imatinib. Nevertheless, all participants will undergo careful surveillance during the initial phase of the study. Baseline analyses will determine whether the participant has had a primary infection with EBV, CMV, or varicella. At each visit, participants will be assessed for signs and symptoms of new or reactivating infections. If there are concerns, including pyrexia of unknown origin, participants will be evaluated for opportunistic infections, including PCR monitoring for EBV and CMV. If a diagnosis of a new or reactivating infection that is clinically significant is confirmed, imatinib treatment will be discontinued until successful treatment and resolution of the infection. In conjunction with an infectious disease consultation, reintroduction of imatinib will be considered.

5.2.8 Pregnancy

Site staff will regularly review the concerns regarding avoidance of pregnancy with participants during the course of the study, especially during the initial 6 months on therapy. Urine pregnancy tests will be conducted at baseline and every following visit while on study drug. Male participants are to use birth control at least 3 months after study drug discontinuation. If, despite these measures, a participant becomes pregnant, imatinib will be permanently discontinued and the participant will be counseled on potential risks to the fetus. Pregnancies of partners of male participants will also be followed.

Given the potential risk to the fetus, while on study drug/placebo, women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must agree to use highly effective methods of contraception.. This contraception should start1 week or more prior to the start of study drug/placebo (noting that the terminal half-life of imatinib is approximately 18 hours, and 5 times this duration is 90 hours or ~4 days)) and continue during the subsequent 6 months of study drug/placebo dosing
Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized

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male partner should be the sole partner for that subject
- Combination of any two of the following (a+b or a+c, or b+c):

a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
b. Placement of an intrauterine device (IUD) or intrauterine system(IUS)
c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

5.2.9 Bone and Mineral Metabolism

Small clinical studies in oncology have identified effects on bone metabolism. Further, in a pilot animal study there is a possible effect of imatinib on growth plate architecture, and in a few case reports and a retrospective analysis of children with CML there is a possible effect of therapy on growth rate (see section 1.5.1.11). Therefore, biochemical markers of bone metabolism will be measured in all subjects. At Visit 0, all subjects less than 18 years of age will have their bone age assessed using the Fels method (plain film) by a central reader who is an expert in skeletal maturation in order to determine their bone age and growth potential. Female subjects with a bone age of less than 14 years and male subjects with a bone age less than 16 years will be considered to have significant remaining growth potential at study entry and referred to in this protocol as a “growing-age participant”. Growth assessments will be performed according to the Schedule of Events.

Growing-age participants will have their Ht-SDS determined via standard reference charts published by CDC (2001). Additional factors that commonly affect growth will be evaluated at regular intervals, to distinguish the potential contribution from these issues versus those that may be attributed to study drug.

Phosphorous and vitamin D supplementation may be needed if any deficiencies are noted, as suggested by Berman et al.152 Given the relatively short-term course of therapy, we do not expect any long-term problems with bone metabolism.

5.2.10 QT Prolongation

All participants will have electrocardiograms (ECGs) performed at Visit -1 (screening) and Visit 1. Participants will not be eligible for the study if QTc is > 450 ms in males or >470 ms in females at Visit -1, If QTc is >480 ms or there is > 60 ms change from the Visit -1 ECG, then study drug will be discontinued. Participants experiencing dizziness or syncope greater than a grade 2 should promptly seek medical attention and obtain an ECG and electrolytes.

5.3 DISCONTINUATION OF STUDY MEDICATION IN AN INDIVIDUAL PARTICIPANT

Study medication according to study specifications will be discontinued for an individual participant if any of the following occurs:

- A discontinuation criterion for imatinib, as noted in section 5.2, is met.
- Clinical evidence of cardiac toxicity, such as congestive heart failure orsignificant cardiac arrhythmias, is observed.
- Pregnancy occurs.
- A severe or serious AE occurs, which, based on the medical judgment of the investigator, prevents a participant from completing the study treatment (see section 8 for classification of AEs).
- The investigator determines that it is in the participant’s best interest to discontinue treatment.
- The participant, or participant’s legal representative, requests that treatment be halted.

Further care will be provided according to the judgment and practice of the investigator.

The participant will be asked to remain in the study and participate in follow-up. If study treatment is discontinued, the medical monitor should be notified.

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5.4 CONCOMITANT MEDICATIONS

Any participants who need to start a concomitant medication, for whatever reason, should contact the study team to review its potential effects on imatinib metabolism. Those who require an emergency therapy will be encouraged to pursue the necessary clinical care, but then contact the study team within 24 hours to review the potential effects on imatinib metabolism. Whenever possible, the recommendation will be to use concomitant medications that do not alter imatinib levels.

5.4.1 Prohibited Medications

Use of cytochrome P450 inducers/inhibitors, unless considered essential by the investigator, are prohibited during the treatment phase. Imatinib is metabolized by the CYP3A4/5 cytochrome P450 enzyme system, and drugs that induce or inhibit this enzyme may alter imatinib levels (see section 1.5.1.12 for a list of inducers and inhibitors).

5.5 DRUG ACCOUNTABILITY

Under federal regulations (21CFR 312.62) an investigator is required to maintain adequate records of the disposition of the investigational product, including the date and quantity of drug that was received, the participants to whom drug was dispensed (participant by participant accounting), and an account of any drug accidentally or deliberately destroyed. The investigator will ensure that the investigational product supplies are stored as specified in the protocol and pharmacy manual in a secured area, with access limited to authorized study personnel as described in the clinical study agreement.

Records for receipt, storage, use, and disposition of the study drug will be maintained by the study sites. A drug-dispensing log will be kept current for each participant and will contain the identification of each participant and the date and quantity of drug dispensed. All remaining unused investigational product will be returned to the sponsor or sponsor's representative after study termination, or destroyed with the permission of the sponsor in accordance with applicable law and study site procedures. If investigational product is to be destroyed locally, the investigator will provide documentation in accordance with sponsor's specifications.

All records regarding disposition of the investigational product will be available for inspection by the clinical trial monitor.

5.6 ASSESSMENT OF COMPLIANCE WITH STUDY MEDICATION

Pill counts will be used to assess participant compliance with daily doses of the study medication.

REFERENCES

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.

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