Jun 11, 2021

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

In 1 collection

Stephen.Gitelman [1], Jeffrey A. Bluestone[2]

[1]Professor of Clinical Pediatrics, Department of Pediatrics University of California, San Francisco Room S-679, Campus Box 0434, 513 Parnassus Avenue, San Francisco, CA 94143;

[2]Professor of Medicine, Pathology, Microbiology & Immunology, University of California, San Francisco, Campus Box 0540, 513 Parnassus Avenue San Francisco, CA 94143

 dx.doi.org/10.17504/protocols.io.bu8knzuw

Gitelman UCSF

Stephen.Gitelman

ABSTRACT

This is Part 1 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 participants with new-onset type 1 diabetes mellitus".

ATTACHMENTS

dngubkeaf.pdf

DOI

dx.doi.org/10.17504/protocols.io.bu8knzuw

PROTOCOL CITATION

Stephen.Gitelman , Jeffrey A. Bluestone 2021. Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). **protocols.io** https://dx.doi.org/10.17504/protocols.io.bu8knzuw

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

Safety, Efficacy, Imatinib, Beta-Cell Function, New-Onset Type 1 Diabetes Mellitus

CREATED

May 22, 2021

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

LAST MODIFIED

Jun 11, 2021

OWNERSHIP HISTORY

May 22, 2021 Urmilas

Jun 03, 2021 Stephen.Gitelman

PROTOCOL INTEGER ID

50156

PARENT PROTOCOLS

Part of collection

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

GUIDELINES

1.1 OVERVIEW:

Type 1 diabetes mellitus (T1DM) results from the autoimmune destruction of insulinproducing ß cells. Although exogenous insulin is widely available, it is not possible for affected individuals to consistently achieve euglycemia with current technology, and thus they are at risk for devastating long-term complications. This phase II study is designed to evaluate the safety and efficacy of imatinib mesylate as a novel therapy for new-onset T1DM. Imatinib is a first–in-class tyrosine kinase inhibitor that has had remarkable success as a therapy for several cancers, including chronic myelogenous leukemia (CML). In preclinical studies, imatinib is one of only a handful of agents that has been shown in the nonobese diabetes (NOD) mouse to induce a durable remission of new-onset diabetes without continuous ongoing therapy. These findings have been extended to the clinical arena, where case reports and smaller studies have shown positive effects of imatinib in patients with autoimmune conditions and for type 2 diabetes. Although the mechanism whereby this agent functions has not been fully elucidated, the possibility that short-term therapy with imatinib can induce tolerance and lead to a durable long-term remission makes it a very attractive potential therapy for new-onset T1DM.

1.2 BACKGROUND:

T1DM is a chronic autoimmune disease in which insulin-producing ß cells are completely destroyed, resulting in a lifelong dependence on exogenous insulin.2-5 Current management of T1DM is not optimal. To avoid long-term complications, affected individuals must maintain near-normal glycemic control by frequent glucose monitoring, and by taking multiple daily doses of insulin (via injection or pump) adjusted for variations in diet and exercise.[6] Such strict glycemic control is rarely achieved with current T1DM management, and can result in recurrent severe hypoglycemia. Thus, it is not possible to fully mimic ß-cell function with current therapies, and there are currently no established treatments that can prevent the autoimmune ß-cell destruction before diagnosis.

After clinical presentation, affected individuals often enter a “honeymoon,” or remission, phase when they are still able to make substantial amounts of insulin.[7-9] Nevertheless, endogenous insulin secretion continues to slowly deteriorate over the first few years of disease, eventually becoming undetectable and necessitating increasing reliance on exogenous insulin. Past studies have demonstrated that preservation of even modest endogenous insulin secretion dramatically improves metabolic control of T1DM, which, in turn, is associated with reduced morbidity and mortality.[10-13] The ultimate goal of this study is to identify a means of blocking further autoimmune destruction of the ß cells, retaining endogenous insulin secretion and thereby improving metabolic control. Eventually, such a therapy may also be used at an even earlier stage to prevent T1DM.

T1DM occurs in those who have an underlying genetic risk in synergy with one or more environmental exposures.[2-5] Increasing evidence suggests that both adaptive and innate immunity may play a role.[14,15] This process is mediated by the progression of a destructive T-cell infiltration of insulin-producing ß cells. Both CD4+ and CD8+ T cells cooperate in the initiation of insulitis and ß-cell destruction occurs via cytokines (e.g., IFNγ, TNFα) and direct

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

cytolytic activity.[2-4,16-19] Development and propagation of this autoimmune destruction is not solely dependent on T cells, with potential roles ascribed to B cells, NK cells, NKT cells, dendritic cells (DCs), and macrophages.[3,20-24] For example, B-cell depletion in the NOD mouse has been shown to prevent and reverse diabetes,[25,26] and in a recent clinical trial subjects with new-onset T1DM treated with rituximab, an anti-CD20 monoclonal antibody (mAb) had slower decline in ß-cell loss than controls.[27] Thus, agents affecting more than one cell type of the immune system, or with effects on inflammation, may have greater efficacy in modulating the autoimmune response.

Several promising studies have shown that interventions shortly after the time of T1DM diagnosis can alter the natural course of the honeymoon phase. Cyclosporine prolongs endogenous insulin secretion, and some participants experienced complete remission.[28,29] However, long-term treatment is limited by toxicity and by the transience of the effects.[30-32] More targeted therapy with a short course of two different preparations of an anti-CD3 mAb have been promising, although not all respond, and the effects wane over time.[33-36] Recent new onset trials with other agents have had mixed results, with some agents causing acute worsening in beta cell function (IL-2 with rapamycin, Long et al, Diabetes, in press), some showing no effect[37,38] and some showing initial preservation but without sustained effects.[27,39] Despite these early successes, there is ongoing concern with the durability of the response, and the safety and tolerability of the agents offered. Thus, there is currently no established, acceptable immunotherapy for new-onset T1DM to preserve endogenous insulin secretion. The limitations may stem from the need for a multi-faceted approach to interdicting the autoimmune response, using either a combination of drugs[40], or a drug that affects multiple different cell types or pathways. The drug proposed in this trial, imatinib, falls into this latter camp.

1.3 SCIENTIFIC RATIONALE

Imatinib mesylate, also known as CGP57148B, STI-571, Gleevec®, or Glivec® (Novartis), is a specific inhibitor of the Abl protein tyrosine kinases (v-Abl, Bcr-Abl, and c-Abl).[41-43] Imatinib's activity against cells bearing the Bcr-Abl translocation, created by the Philadelphia chromosome abnormality, has resulted in a unique niche for the treatment of CML.[44-48] However, imatinib's activity is not limited to Abl, as it also inhibits other constitutively activated tyrosine kinases, such as platelet-derived growth factor receptor (PDGFR), c-kit (CD117), macrophage colony stimulating factor receptor (c-fms), Abl-related gene, and Lck, whereas other kinases are probably not affected.[49-54] The inhibitory activity against c-kit and PDGFR has resulted in imatinib's expanded use as a therapy for gastrointestinal stromal tumors (GIST), [55] eosinophilic disorders, [56] and systemic mast cell disease.[56,57].

In addition to its remarkable effect on malignant cells, imatinib has been shown to affect various arms of the immune system. Imatinib treatment may lead to impaired T-cell function and decreased DC number in CML patients,[58-60] although other studies have not documented such effects.[61-64] Similarly, while some reports suggest that imatinib enhances DC function both in human[65,66] and mouse,[67-69] other studies demonstrated that relatively high concentrations (1–5 μM) inhibited the development and the functional capacity of human or mouse DCs,[70-72] as well as human monocytes/macrophages.[73-75] Several investigators have now shown that imatinib has significant anti-inflammatory properties in different mouse models. Wolf et al demonstrated in a mouse model of acute hepatic inflammation that imatinib inhibits tumor necrosis factor-alpha (TNFα) production in macrophages, conferring a strong anti-inflammatory effect.[76] Dietz et al noted that delayed-type hypersensitivity was reduced in mice treated with imatinib.[77]

Most recently, it has become clear that imatinib can function as an effective immunosuppressive drug. In preclinical studies, imatinib efficiently prevents disease and induces remission of mouse and rat models of autoimmune arthritis.[78-80] Moreover, this drug inhibits collagen-induced arthritis effectively in mice and blocks PDGFRmediated signaling in synovial fibroblasts obtained from rheumatoid arthritis patients.[81- 83] Efficacy in rheumatoid arthritis may also result from effects on mast cells: treatment of rheumatoid synovia in vitro with imatinib inhibits c-kit and induces apoptosis of mast cells.[84] Furthermore, imatinib treatment ameliorates autoimmune nephritis in two mouse models of lupus.[85,86] In studies of scleroderma, Soria et al reported that imatinib limits dermal fibroblast proliferation.[87] Imatinib reduces production of extracellular matrix and suppresses experimental fibrosis,[88] and prevents fibrosis in different models of systemic sclerosis.[87] Imatinib

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

inhibits PDGF-mediated responses related to the development of intimal hyperplasia in giant cell arteritis.[89] Imatinib may also be effective in the treatment of anti-neutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA), based on inhibition of T-cell activation in samples taken from affected patients.[90]

These findings have been extended to the clinical arena, where a few case reports and a phase I study show positive effects of imatinib in patients with rheumatoid arthritis.[79,91-94] Early studies suggest that imatinib may have a role in the treatment of systemic sclerosis.[95-98] Imatinib therapy improved cutaneous sclerosis and inflammatory manifestations of the disease in 3 treated subjects, [96,97] and a specific gene signature of imatinib response has been identified.[96] Seven trials evaluating the efficacy of Imatinib in systemic sclerosis are now posted on the clinicaltrials.gov web site. Imatinib was also effective and well tolerated in a phase I study of 6 patients with active spondyloarthritis.[99] There is a case report of a patient with bullous pemphigoid, the most frequent autoimmune blistering dermatosis, with eosinophilia and a deletion consistent with hypereosinophilic syndrome, who responded to imatinib therapy.[100] There is one case report of imatinib therapy inducing a long-standing remission in a patient with Crohn's disease, without significant side effects.[101] Imatinib has also been reported to treat intractable psoriasis in a patient who was receiving this agent for GIST.[102]

Although the aforementioned studies suggest efficacy, the mechanisms are unclear. In vitro studies suggest that imatinib may have direct effects on T-cell, B-cell, and antigenpresenting cell signaling and function. Imatinib can inhibit human T-cell proliferation in vitro without inducing apoptosis,[77,103,104] and analysis of the TCR-induced signaling cascade revealed a reduced phosphorylation of ZAP-70, LAT, Lck and ERK1/2, as well as reduced levels of activated NFκB.77,[104,105] Interestingly, Lck has been suggested as a direct target of imatinib.[52] Studies in the mouse demonstrated that imatinib could impair memory CD8+ T-cell development but did not affect the primary response and cytotoxic activity or induce apoptosis.[106-108] However, lytic function of human CD8+ T cell has recently been shown to be inhibited by imatinib.[109]

The proposed trial represents a unique approach to the treatment of T1DM and will provide critical validation of the hypothesis that a new class of kinase inhibitors, represented by the first-in-class compound imatinib, will demonstrate a novel therapy for T1DM. The possibility that short-term therapy with imatinib can induce tolerance and lead to a durable long-term remission makes it a very attractive potential therapy for patients with new-onset T1DM. If this therapy is safe and effective, then its use can be expanded to other autoimmune disorders, and possibly to T1DM prevention.

1.4 PRECLINICAL AND CLINICAL EXPERIENCE:
1.4.1 Preclinical Studies:
1.4.1.1 Studies in the NOD Mouse:

The known mechanisms of imatinib action and observations in other autoimmune settings suggest that imatinib may have an important role in treating T1DM. Hagerkvist et al noted that imatinib prevents T1DM in the NOD mouse when administered from 9 to 35 weeks of life; it did not affect the extent of islet inflammation when given from 3 to 9 weeks of age or when treated out to 35 weeks, but the ß-cell area is significantly greater in treated animals.[110] They also examined specific effects of imatinib on the ß cell. Three doses of imatinib partially protect against T1DM in streptozotocin (STZ)- injected mice. It also protects cultured islets from various apoptosis-promoting agents, including pro-inflammatory cytokines, nitric oxide, and STZ.[110,111] Thus, imatinib appears to act on multiple levels in diabetes, including reduction of insulin resistance and prevention of ß-cell apoptosis. The authors concluded that imatinib enhances ß-cell survival via a mechanism similar to ischemic preconditioning, as they found NFkB activation, increased nitric oxide and reactive oxygen species production, and depolarization of the inner mitochondrial membrane.

1.4.1.1.1 Prevention of T1DM

Treatment of prediabetic NOD mice starting at 12 weeks of age (a stage when insulitis is firmly established)[112] with imatinib orally once a day at 1.5

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

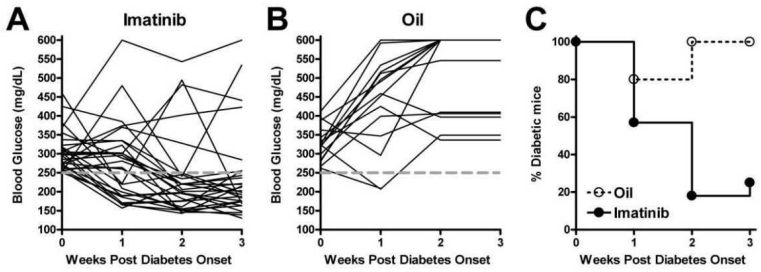

Figure 1. Induction of diabetes remission. Imatinib or oil treatment was initiated at the time of disease onset (blood glucose >250 mg/dL) and continued for 3 weeks. Individual glucose readings for imatinib- (*A*) and oil-treated mice (*B*) are shown. (*C*) The percentage of diabetic mice is shown for each group : imatinib n=28, oil n=15. From Louvet et al.[112]

mg/mouse for 7

weeks led to complete protection from hyperglycemia during treatment, whereas half of the control mice developed diabetes. After cessation of treatment, only ~40% of the imatinib-treated animals became progressively diabetic. The majority of the mice remained nondiabetic at more than 50 weeks of age. Treatment of mice with cyclophosphamide (CY)-induced diabetes (a more robust model with rapid onset of disease) resulted in only ~30% of imatinib-treated animals developing diabetes within 3 weeks after CY injection, in contrast to 85% of the control mice. These results confirmed that imatinib can prevent T1DM.

1.4.1.1.2 Remission Induction

Many agents prevent T1DM in the NOD mouse before the development of insulitis,[20,113] but only a handful of agents are successful in inducing remission in overtly diabetic NOD mice. Louvet et al[112] found that only 1 week after initiation of treatment, imatinib reversed diabetes in more than 40% of diabetic animals (Figures 1A and 1C) and after 2 weeks the remission rate jumped to ~80% of the mice (n = 28). The effect of imatinib was most notable in mice with glucose levels that were modestly elevated at diagnosis (250–350 mg/dL) but was also effective in mice with glucose levels > 300–450 mg/dL, although less so. Mice treated with vehicle alone did not reverse diabetes (Figures 1B and 1C).

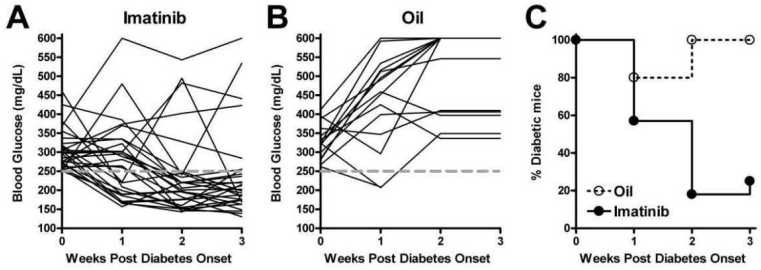

Figure 1. Induction of diabetes remission. Imatinib or oil treatment was initiated at the time of disease onset (blood glucose >250 mg/dL) and continued for 3 weeks. Individual glucose readings for imatinib- (*A*) and oil-treated mice (*B*) are shown. (*C*) The percentage of diabetic mice is shown for each group : imatinib n=28, oil n=15. From Louvet et al.[112]

1.4.1.1.3 Tolerance Induction:

With cessation of imatinib therapy at 3 weeks, all mice became hyperglycemic within 10 weeks (Figure 2A). However, by increasing treatment duration from 3 weeks to 10 weeks the majority of the mice remained euglycemic (Figure 2B).[112] Thirty-five weeks after initiation of therapy, ~50% of imatinib-treated animals had reversed from diabetes into a state of long-term tolerance without the need of continuous treatment.

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

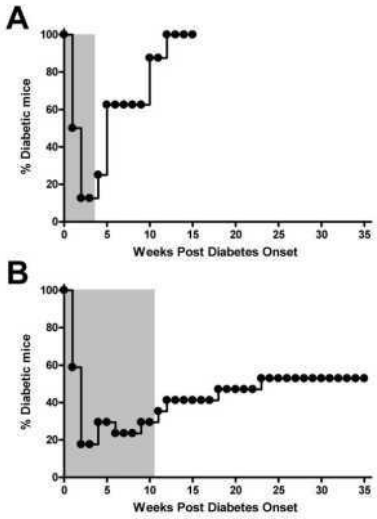

Figure 2. Long-lasting remission of diabetic NOD mice. Imatinib treatment (*gray shaded area*) was initiated at the time of disease onset and continued for (*A*) 3 weeks (n=8) or (*B*) 10 weeks (n=17). From Louvet et al.[112]

1.4.1.1.4 Leukocyte Infiltration of the Pancreas:

Treatment of prediabetic NOD mice for variable periods of time with imatinib did not prevent insulitis.[112] There were subtle differences in severe and mild insulitis in the drug-treated versus control islets, but these findings were not statistically significant, in accord with prior studies.[110] Similarly, pancreatic islets from long-term normoglycemic mice after cessation of imatinib treatment still harbored significant insulitis. Thus, while preventing clinical disease, imatinib does not eliminate leukocyte infiltration of the pancreas. It should be noted that this observation is different from what has been observed for anti-T-cell agents such as Thymoglobulin and anti-CD3, which clear the islets of infiltration, suggesting a different mechanism of action.[114,115]

1.4.1.1.5 Relevance of Tyrosine Kinase–blocking Activity:

As documented previously,[116] imatinib can affect a series of tyrosine kinases in vitro including abl, c-kit, c-fms, and PDGFR. To pinpoint the relevant kinases in T1DM therapy, different TK-blocking agents that share targets with imatinib have been tested.[112] These studies suggest that the dramatic effects of imatinib in the reversal of diabetes are not due to a single drug activity but due to the combination of the anti-inflammatory effects short term, due at least in part to its PDGFR antagonism, combined with longer term effects, perhaps due to its c-abl- and c-kit-specific activities. A clinical case report (see section 1.3.2) lends further support for this proposal.[117]

1.4.1.2 Studies in Rat and Mouse Models of T2DM:

Hagerkvist et al reported that imatinib normalizes peripheral insulin resistance in rats fed a high-fat diet.[118] Han et al extended these observations in the diabetic dyslipidemia (db/db) mouse, noting that imatinib reduces insulin resistance and induces diabetes remission.[119] Liver steatosis and serum transaminitis are markedly reduced in treated animals. Imatinib also decreased TUNEL+ apoptotic ß cells and increased BrdU+ ß- cell numbers. A unifying explanation for these effects is that imatinib ameliorates endoplasmic reticulum (ER) stress: ER stress appears to play an important role in insulin resistance, and Abl kinase, an imatinib target, has been reported to play a role in this process.[120] Indeed, a variety of ER stress markers in the liver and adipose tissue were reduced by imatinib treatment of these animals. Recent findings that kinase inhibition of IRE1α ameliorates ER stress and consequent apoptosis[121] lends additional support to the potential role of imatinib in this process.

1.4.2 Clinical Studies in Patients with Diabetes:

Since approved for treatment of CML, several case reports and small case series have appeared describing

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

patients with T2DM who have experienced significant improvement or resolution on imatinib.[122-124] Reductions in cholesterol and triglycerides have also been described in treated patients.[125]

These changes have not been ascribed to significant effects with decreased appetite or weight loss. Fitter et al[126] have further evaluated mechanisms whereby metabolic control improves for subjects with T2DM treated with imatinib. They have noted that adiponectin levels increase ~ 3-fold within 3 months of initiating imatinib, and remain elevated with on-going therapy out to 12 months. This adipokine increases glucose uptake and fatty acid oxidation in muscle, and decreases hepatic gluconeogenesis; low adiponectin levels are associated with increased insulin resistance and higher risk for T2DM.

In a case report of another tyrosine kinase inhibitor, a 64-year-old man with metastatic renal cell carcinoma was started on sunitinib 8 months after the diagnosis of diabetes.[117] He was presumed to have T1DM, based on strongly positive GAD antibody titers. After ~15 weeks on sunitinib, the insulin dose was decreased, until he discontinued insulin altogether at ~45 weeks on sunitinib. Sunitinib was discontinued at about that same time, but glycemic control has remained near normal over the ensuing 30 weeks, with persisting elevation of GAD antibody titers. His weight remained stable over the treatment period.

1.5 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS FOR HUMAN PARTICIPANTS

1.5.1 Risks

1.5.1.1 Overview

There is an extensive safety experience in patients treated with imatinib for CML and GIST (see larger clinical trials in Refs. [45,47,55,127-131] and the package insert at http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf) Overall, imatinib has been well tolerated in clinical trials. Adverse events (AE) are typically mild to moderate (grades 1 to 2) and manageable without dosage reduction or permanent discontinuation of therapy. The most common side effects include gastrointestinal reactions (nausea, vomiting, and diarrhea), edema, muscle cramps, and rash. Hematological toxicities (thrombocytopenia, neutropenia, and anemia) are dosedependent and reversible, and noted much more frequently in CML than in GIST, suggesting they relate in large part to the underlying disease. Specific issues are discussed in more detail below. These side effects tend to be more noticeable in older and sicker patients who are on higher doses of imatinib. Many of these adverse events may improve spontaneously while continuing therapy at the same dose. It is difficult to extrapolate fully from the past safety and tolerability experiences in cancer to a diabetes setting, in which our study participants will be younger, will be carefully selected so as not to have concurrent or chronic medical problems, and will be on lower doses of the drug and for a shorter duration. Our expectation, however, is that the therapy will be even better tolerated than in other settings in which it has been traditionally used (B. Druker, Oregon Health Sciences University, personal communication). The published and unpublished experience has been that imatinib is generally better tolerated in younger patients, including children.132-135 No AEs unique to children have been reported, with the possible exception of transient, reversible effects on growth rate (as detailed in section 1.5.1.11).

1.5.1.2 Gastrointestinal Reactions

Nausea constitutes the most common side effect of therapy. It has been noted in up to 40%–60% of subjects with CML or GIST, and it is usually mild, grade 1, and dose related. Nausea occurs much more commonly when the drug is taken on an empty stomach, and can be avoided when taken with food. Ingestion with food has not been shown to affect pharmacokinetic parameters. Diarrhea is also experienced by some patients, possibly from imatinib blockade of c-kit, and is often dose related.

1.5.1.3 Edema

Edema is present in about half of patients on imatinib. It is usually superficial, mild to moderate in nature, and does not require specific therapy. It usually manifests as periorbital edema and is most noticeable first thing in the morning. Edema in the lower extremities is noted much less frequently. More marked issues with fluid retention, such as pulmonary edema or ascites, occur rarely, and have typically been limited to those with more advanced stages of CML. This issue generally occurs at higher doses, and in elderly patients, and has been less common in children.

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

1.5.1.4 Cutaneous Reactions

Cutaneous reactions have been reported in ~30% of patients during imatinib treatment. The rashes are often pruritic, and most commonly erythematous, maculopapular lesions on the forearms and trunk, and sometimes also involve the face. The rashes are usually mild (grades 1–2) and self-limited. About 3% are higher grade, and again are usually associated with higher doses of therapy. Severe exfoliative rashes have been noted in 1 in 500 treated subjects, and they usually occur early in the course of treatment. Imatinib treatment has been associated on rare occasions with induction of vitiligo-like lesions, which may be related to blockade of c-kit in melanocytes.136,137 This finding appears to increase with dose and duration of treatment, and is reversible with dose reduction or discontinuation. Paradoxically, a patient with vitiligo has been described who had repigmentation of his lesions while on imatinib treatment for GIST.138

1.5.1.5 Muscle Cramps, Bone Pain, Arthralgias

Arthralgias affect 25%–50% of treated patients. As with other issues, this is usually mild to moderate, and manageable without reduction of the drug dose. Cramps usually occur in the hands, feet, calves and thighs, and tend not to change over time in terms of location, frequency, and intensity. Ionized calcium and magnesium levels are normal. Bone pain and arthralgias are reported typically early in the course of therapy and usually subside after several months.

1.5.1.6 Hepatotoxicity

Liver toxicity, if an issue, usually emerges during the first few months of therapy, but can be a late finding. Frequent monitoring of liver function is suggested during therapy. Grade 1 elevations in transaminases occur in up to 10% of treated patients and often normalize while continuing on therapy. Grade 3 events have been reported in 2%–5% of subjects in GIST and CML trials, but these events may be confounded by a variety of other factors, including leukemic liver infiltration. For grade 3 events in oncology settings, therapy is temporarily interrupted. Imatinib is permanently discontinued for grade 3 events that recur with drug re-challenge.

1.5.1.7 Myelosuppression

The development of myelosuppression is much more common in CML than GIST, and may relate to the underlying effects of the cancer on the bone marrow. In the phase II study of imatinib for GIST, anemia (9% of subjects, 2% grades 3 or 4), neutropenia (7% of subjects, 5% grade 3 or 4), and leukopenia (5% of subjects, 1% grades 3 or 4) were the most commonly reported findings; grades 3 or 4 thrombocytopenia was noted in <1%. Complete blood counts with differential will be monitored at the same time points as liver function tests. For myelosuppression of grade 3 or higher severity in oncology settings, therapy is temporarily interrupted, and permanently discontinued for grade 3 events that recur with drug re-challenge.

1.5.1.8 Cardiac Toxicity

Prior concern was raised that imatinib may induce cardiac dysfunction, based on a report of 10 subjects with left ventricular dysfunction and congestive heart failure.139 The ejection fraction for these subjects dropped significantly during the course of imatinib therapy, but the authors did not report the size of the underlying cohort from which these cases were derived, nor did they report baseline cardiac function, or other physiological risk factors that might be associated with cardiac dysfunction. A subsequent retrospective review of a large database of 942 GIST patients treated with 400–800 mg of imatinib for a median of 24 months revealed only 2 patients (0.2%) who may have had a cardiotoxic effect from this drug.140 Atallah et al reported that 0.6% of 1276 patients (median age 70) treated with imatinib developed congestive heart failure, and half of these continued therapy.141 The cases typically occurred in elderly patients with preexisting cardiac conditions. A recent study in knockout mice revealed that PDGFR-β signaling is required for the cardiac response to pressure overload-induced stress.142 This provides a mechanistic basis for the observation that cardiac toxicity induced by PDGFR inhibitors, such as imatinib, is generally observed only in patients with preexisting cardiac conditions. Druker (personal communication) has not noted any cardiac issues in treatment of over 1000 patients with imatinib, with the exception of 2 patients over age 65 who developed congestive heart failure; thus, aside from a careful past medical history he does not suggest routine cardiac studies for subjects on imatinib. The relatively short course of proposed treatment and younger, otherwise healthy population would suggest that this will not be an issue in this trial. Subjects enrolled in this trial will have careful baseline history and physical examination to ensure no

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

preexisting cardiac problems.

1.5.1.9 Infectious Disease

Imatinib has been well tolerated, and patients receiving chronic therapy do not appear to be abnormally susceptible to viral infections or opportunistic infections. [45,47,55,127,128,131] Further reassurance comes from evaluation in a mouse model in which imatinib selectively impaired expansion of memory cytotoxic T cells but the expansion of naïve cytotoxic T-cells (CTLs) in response to viral infection in vitro and in vivo was not impaired.107

1.5.1.10 Reproductive Toxicity

Despite the growing clinical experience with imatinib in CML and GIST, there is still only limited data on the effects of imatinib on fertility and/or pregnancy. Animal studies have shown that this drug is teratogenic in rats but not rabbits (Gleevec IB). Spermatogenesis is impaired in rats, dogs, and monkeys. Female rats receiving imatinib doses of 45 mg/kg, which approximates the usual clinical dose of 400 mg/day, experience significant post-implantation loss, including increased fetal resorption, stillbirth, and early pup mortality. It does not appear to cause chromosome damage. Exposure to doses of 100 mg/kg (approximating a clinical dose of 800 mg/day) during organogenesis results in teratogenic effects, with exencephaly or encephalocele, and absent or reduced frontal and parietal bones. Based on these studies, it has been classified as a class D drug. However, there have been a series of case reports and small series reporting normal outcomes following pregnancies.[143-151] The largest compilation of clinical experience is from a retrospective chart review of 180 women exposed to drug during pregnancy; outcome data were available for 125.150 Of these, 50% delivered normal children and 28% had elective terminations (3 following the identification of abnormalities). Twelve infants had abnormalities identified, 3 with a similar complex of malformations. There did not appear to be a higher rate of spontaneous abortion. Thus, although most fetuses exposed to imatinib appear to be unaffected, there is a risk for potential malformation. In light of these findings, investigators need to ensure that all participants avoid pregnancy.

1.5.1.11 Bone and Mineral Metabolism

One small sub-study has noted hypophosphatemia with increased PTH, low normal serum calcium, and increased urinary phosphorous in patients treated with imatinib.152 The authors postulate that this is an effect mediated by PDGFR inhibition. Further studies in vivo and in vitro suggest that short-term therapy with imatinib (on the order of 3-6 months) causes an uncoupling of bone turnover, with activation of bone formation via promotion of osteoblast differentiation, and inhibition of resorption by inhibition of osteoclastogenesis and promotion of osteoclast apoptosis.[153]

A recent study in rats indicated that imatinib treatment (4–12 weeks duration) resulted in narrowing or premature closure of the growth plate in the proximal tibia, although the animals were not assessed for a follow-up period after drug was withdrawn.[154] Three recently published case studies report decelerated growth in juvenile CML patients undergoing imatinib therapy.[155-157] Notably, one of the patients progressed through puberty and reached appropriate final adult height for family while being treated continuously with imatinib[156]; another patient experienced growth acceleration following discontinuation of imatinib[155], but final height was not reported [155]

In the initial reports from the pediatric CML trials with imatinib, no growth or bone metabolism issues were reported.[132-135,158] Following the case reports noted above, Japanese investigators performed a retrospective analysis of 48 children with CML treated with imatinib as a first line therapy for a median of 34 months[159]. They noted that growth rate decreased in pre-pubertal children (defined as girls < age 9 years, boys < 11 years), with a median decrease after 1 year of ~0.5 in height standard deviation score (Ht-SDS) for chronological age, and further progressive decrement with on-going therapy. However, the growth rate improved during puberty, and children who initiated therapy at a pubertal age appeared to have little or no impact on growth rate. These growth issues may be confounded by a variety of issues associated with a chronic illness such as CML, which in and of itself may impact growth rate, and one should note that decreased growth rate is associated with alternate therapies for CML, such as bone marrow transplantation[160].

1.5.1.12 Drug Interactions

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

Imatinib is metabolized by the CYP3A4/5 cytochrome P450 enzyme system. Drugs that induce or inhibit this P450 will affect imatinib levels, and should be used with caution, and if possible avoided, during the course of imatinib therapy. Major CYP3A4/5 inducers may decrease imatinib levels; these include carbamazepine, dexamethasone, phenytoin, phenobarbital, progesterone, rifampin, and St. John's wort. Major CYP3A4/5 inhibitors, which will serve to increase imatinib levels, include cimetidine, erythromycin, fluoxetine, ketoconazole, ritonavir, itraconazole, verapamil, and grapefruit juice. Participants who require chronic therapy with any of these agents will be excluded from participation.

1.5.1.13 Malignancies

On-going pharmaco-vigilance data is being collected to assess risk for malignancy following imatinib exposure (see data on file, Gleevec IND 55,666). An integrated review of safety data from imatinib oncology clinical trials suggests that there may be an increased frequency of genito-urinary malignancies. However, the effect is not statistically significant, and it is limited to those subjects treated for > 2 years. Thus, we will exclude any subjects with prior malignancy, and will carefully monitor genitourinary risk throughout the study with serial urinalyses and prostate specific antigen (for male participants) When rats are treated with imatinib for 2 years, they had a shortened lifespan, and higher risk for developing cancers in the kidneys, bladder, urethra, clitoris, small intestine, parathyroid glands, adrenal glands, and stomach. The relevance of these findings to humans is not known.

1.5.2 Potential Risks and Benefits of Trial Participation for Children

Imatinib has been used to treat Ph+ CML in children as young as age 3, and is FDA approved for this indication .[132,134,135] Smaller trials have also been conducted in children with Ph positive acute lymphoblastic leukemia and some brain tumors[133,161,162] . Doses of 260-340 mg/m2 of imatinib in the pediatric population achieved a similar area under the curve (AUC) to the 400-mg dosing in adults; thus, we plan to employ such dosing in younger or smaller participants enrolled in this trial, offering whichever is the smaller of these two doses to pediatric participants. The safety profile was similar to that in adults, except that there were fewer reports of musculoskeletal pain and peripheral edema. As described in section 1.5.1.11, there is a potential concern about the effects of imatinib on growth, based on preclinical data several case reports, and a retrospective study of pre-pubertal Japanese children with CML (defined as girls < 9 and boys < 11 years of age)[159]. With these initial observations in mind, we will limit enrollment to ages 12 and older for this trial. At age 12, girls have completed on average 92% of their growth, and boys 83% of their final adult height[163], thus limiting potential effects of drug on final height. Furthermore, as opposed to the studies referenced above in cancer, subjects in this trial will only have a brief 6-month exposure period on study drug, at a modest dose, and thus will not have the long term continuous exposure that has been associated with progressive slowing in growth rate for pre-pubertal children. As detailed in section 5.2.9, effects on growth rate will be carefully assessed in subjects with significant remaining growth potential at study entry, and all subjects will have frequent monitoring of bone metabolism and bone turnover markers. One of the study stopping rules relates to impact of imatinib on growth rate (Section 3.7).

As one of the most common chronic childhood diseases, T1DM is a particular burden to children and their families. While T1DM can occur into adulthood, the worldwide incidence of T1DM is increasing rapidly in children younger than 15 years, as recently documented by the WHO Diamond Project.[164] During the period 1995–1999, the global annual increase in childhood T1DM was 3.4% but was as high as 5.3% in North America.[164] In Europe, the EURODIAB study group has found the greatest rate of increase in the 0-4 years age group and is predicting a doubling in the number of new cases in children younger than 5 years in the next decade.[165] Overall, prevalence of T1DM in children under age 15 in Europe is predicted to rise from 94,000 in 2005 to 160,000 in 2020.[165] In contrast, the incidence of T1DM in young adults over age 15 is not increasing.[165] For these reasons, there is considerable interest in identifying safe and effective interventions that can modify the course of T1DM in pediatric populations. Successful initial preservation of β-cell function in pediatric populations has recently been reported for several treatment modalities.[27,33-36,39]

Evaluation of new interventions for T1DM in adults may not be informative about their success in children. It is known that the rate of β-cell decline is different in children versus adults (Greenbaum et al, Diabetes)[178], and therefore lack of efficacy of a treatment in adults is not necessarily predictive of efficacy in children.[27,36] There are currently no approved interventions for new-onset T1DM. In contrast to many interventions currently being

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

studied in the pediatric population, imatinib is approved for use in children and has an extensive clinical safety record. Imatinib is also unique among agents being studied for new-onset T1DM in that is an oral drug, which has special relevance in the pediatric age group.

1.5.3 Potential Benefits

In this study, all participants will receive intensive diabetes management aimed at achieving near-normal metabolic control per the standard American Diabetes Association (ADA) guidelines.[1] Although intensive diabetes management is recommended for all patients with T1DM, it is not always available to all subjects in the community. The Diabetes Control and Complications Trial (DCCT) research group documented that improved metabolic control lowers the risk for long-term complications.[6] The means to achieve this improved control in the DCCT has become the idealized standard of care, with clinical management and education provided by a diabetes specialty team. It should be noted that such care may not necessarily be available to those outside the study, and those who are not seen by a diabetes specialty team may have worse outcomes over time.[166]

Improved metabolic control early in the course of T1DM will have a long-standing effect on lowering the risk for long-term complications for many years to follow; i.e., there appears to be a “metabolic memory” that influences later risk. This effect has been documented in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the long-term follow-up of the DCCT cohort. [6,12,167-170] Although the conventional group (with less stringent metabolic control) and the intensive group (with near-normal metabolic control) have had comparable HbA1C levels since the end of the formal DCCT study, the intensive group continues to have significantly lower risk for complications 10 years later.

An additional benefit that may be realized by all participants is that maintaining nearnormal glycemic control through intensive diabetes management may, in and of itself, lead to the preservation of ß-cell function.[10,11,13,171] The benefits of endogenous insulin secretion, even if one needs to continue exogenous insulin therapy, have been demonstrated in a number of studies, including the DCCT, where those subjects with residual C-peptide had improved metabolic control, with lower risk for severe hypoglycemia and less likelihood of microvascular complications. Finally, the treatment group may have significant benefits from participation even if imatinib therapy has only modest effects on the preservation of endogenous insulin secretion, which is what was noted in the new-onset T1DM studies with anti-CD3 mAb therapy.[34,172]

REFERENCES

1. Association AD. Standards of medical care in diabetes--2012. Diabetes Care. Jan 2012;35 Suppl 1:S11-63
2. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. N Engl J Med. Nov 24 1994;331(21):1428-1436.
3. Bach JF. Insulin-dependent diabetes mellitus as an autoimmune disease. Endocr Rev. Aug 1994;15(4):516-542.
4. Castano L, Eisenbarth GS. Type-I diabetes: a chronic autoimmune disease of human, mouse, and rat. Annu Rev Immunol. 1990;8:647-679.
5. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. Apr 2010;464(7293):1293-1300.
6. Group TDCaCTR. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. Sep 30 1993;329(14):977-986.
7. Madsbad S, Faber OK, Binder C, McNair P, Christiansen C, Transbol I. Prevalence of residual beta-cell function in insulin-dependent diabetics in relation to age at onset and duration of diabetes. Diabetes. 1978;27 Suppl 1:262-264.
8. O'Meara NM, Sturis J, Herold KC, Ostrega DM, Polonsky KS. Alterations in the patterns of insulin secretion before and after diagnosis of IDDM. Diabetes Care. Apr 1995;18(4):568-571.
9. Steele C, Hagopian WA, Gitelman S, et al. Insulin secretion in type 1 diabetes. Diabetes. Feb 2004;53(2):426-433.
10. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. Ann Intern Med. Apr 1 1998;128(7):517-523.
11. Group TDCaCTR. Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual beta-cell function: observations during eligibility testing for the Diabetes Control and Complications Trial (DCCT). J Clin Endocrinol Metab. Jul 1987;65(1):30-36.
12. Nathan DM, Zinman B, Cleary PA, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years'

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med. Jul 27 2009;169(14):1307-1316.
13. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care. Mar 2003;26(3):832-836.
14. Bach JF, Bendelac A, Brenner MB, et al. The role of innate immunity in autoimmunity. J Exp Med. Dec 20 2004;200(12):1527-1531.
15. Zipris D. Innate immunity and its role in type 1 diabetes. Curr Opin Endocrinol DiabetesObes. Aug 2008;15(4):326-331.
16. Bendelac A, Carnaud C, Boitard C, Bach JF. Syngeneic transfer of autoimmune diabetes from diabetic NOD mice to healthy neonates. Requirement for both L3T4+ and Lyt-2+ T cells. J Exp Med. Oct 1 1987;166(4):823-832.
17. Christianson SW, Shultz LD, Leiter EH. Adoptive transfer of diabetes into immunodeficient NOD-scid/scid mice. Relative contributions of CD4+ and CD8+ T-cells from diabetic versus prediabetic NOD.NON-Thy-1a donors. Diabetes. Jan 1993;42(1):44-55.
18. Kagi D, Odermatt B, Seiler P, Zinkernagel RM, Mak TW, Hengartner H. Reduced incidence and delayed onset of diabetes in perforin-deficient nonobese diabetic mice. J Exp Med. Oct 6 1997;186(7):989-997.
19. Serreze DV, Leiter EH, Christianson GJ, Greiner D, Roopenian DC. Major histocompatibility complex class I-deficient NOD-B2mnull mice are diabetes and insulitis resistant. Diabetes. Mar 1994;43(3):505-509.
20. Anderson MS, Bluestone JA. The NOD mouse: a model of immune dysregulation. Annu Rev Immunol. 2005;23:447-485.
21. Dotta F, Fondelli C, Falorni A. Can NK cells be a therapeutic target in human type 1 diabetes? Eur J Immunol. Nov 2008;38(11):2961-2963.
22. Eisenbarth GS. Type 1 diabetes: molecular, cellular and clinical immunology. Adv Exp Med Biol. 2004;552:306-310.
23. Serreze DV, Silveira PA. The role of B lymphocytes as key antigen-presenting cells in the development of T cell-mediated autoimmune type 1 diabetes. Curr Dir Autoimmun. 2003;6:212- 227.
24. Trembleau S, Penna G, Bosi E, Mortara A, Gately MK, Adorini L. Interleukin 12 administration induces T helper type 1 cells and accelerates autoimmune diabetes in NOD mice. J Exp Med. Feb 1 1995;181(2):817-821.
25. Hu CY, Rodriguez-Pinto D, Du W, et al. Treatment with CD20-specific antibody prevents and reverses autoimmune diabetes in mice. J Clin Invest. Dec 2007;117(12):3857-3867.
26. Xiu Y, Wong CP, Bouaziz JD, et al. B lymphocyte depletion by CD20 monoclonal antibody prevents diabetes in nonobese diabetic mice despite isotype-specific differences in Fc gamma R effector functions. J Immunol. Mar 1 2008;180(5):2863-2875.
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.
28. Feutren G, Papoz L, Assan R, et al. Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset. Results of a multicentre double-blind trial. Lancet. Jul 19 1986;2(8499):119-124.
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.
30. Bougneres PF, Landais P, Boisson C, et al. Limited duration of remission of insulin dependency in children with recent overt type I diabetes treated with low-dose cyclosporin. Diabetes. Oct 1990;39(10):1264-1272.
31. Feldt-Rasmussen B, Jensen T, Dieperink H, et al. Nephrotoxicity of cyclosporin A in patients with newly diagnosed type 1 diabetes mellitus. Diabet Med. Jun 1990;7(5):429-433.
32. Martin S, Schernthaner G, Nerup J, et al. Follow-up of cyclosporin A treatment in type 1 (insulindependent) diabetes mellitus: lack of long-term effects. Diabetologia. Jun 1991;34(6):429-434.
33. Herold KC, Hagopian W, Auger JA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N.Engl.J Med. 2002;346(22):1692-1698.
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.
35. Keymeulen B, Vandemeulebroucke E, Ziegler AG, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. N Engl J Med. Jun 23 2005;352(25):2598-2608.
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.

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

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.
40. Matthews JB, Staeva TP, Bernstein PL, Peakman M, von Herrath M, Group I-JTDCTA. Developing combination immunotherapies for type 1 diabetes: recommendations from the ITNJDRF Type 1 Diabetes Combination Therapy Assessment Group. Clin Exp Immunol. May 2010;160(2):176-184.
41. Buchdunger E, Zimmermann J, Mett H, et al. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. Cancer Res. Jan 1 1996;56(1):100- 104.
42. Deininger MW, Goldman JM, Lydon N, Melo JV. The tyrosine kinase inhibitor CGP57148B selectively inhibits the growth of BCR-ABL-positive cells. Blood. Nov 1 1997;90(9):3691-3698.
43. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med. May 1996;2(5):561-566.
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.
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.
49. Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther. Oct 2000;295(1):139-145.
50. Carroll M, Ohno-Jones S, Tamura S, et al. CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins. Blood. Dec 15 1997;90(12):4947-4952.
51. Dewar AL, Zannettino AC, Hughes TP, Lyons AB. Inhibition of c-fms by imatinib: expanding the spectrum of treatment. Cell Cycle. Jul 2005;4(7):851-853.
52. Fabian MA, Biggs WH, 3rd, Treiber DK, et al. A small molecule-kinase interaction map for clinical kinase inhibitors. Nat Biotechnol. Mar 2005;23(3):329-336.
53. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood. Aug 1 2000;96(3):925-932.
54. Okuda K, Weisberg E, Gilliland DG, Griffin JD. ARG tyrosine kinase activity is inhibited by STI571. Blood. Apr 15 2001;97(8):2440-2448.
55. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. Aug 15 2002;347(7):472-480.
56. Pardanani A, Reeder T, Porrata LF, et al. Imatinib therapy for hypereosinophilic syndrome and other eosinophilic disorders. Blood. May 1 2003;101(9):3391-3397.
57. Pardanani A, Elliott M, Reeder T, et al. Imatinib for systemic mast-cell disease. Lancet. Aug 16 2003;362(9383):535-536.
58. Boissel N, Rousselot P, Raffoux E, et al. Defective blood dendritic cells in chronic myeloid leukemia correlate with high plasmatic VEGF and are not normalized by imatinib mesylate. Leukemia. Oct 2004;18(10):1656-1661.
59. Gao H, Lee BN, Talpaz M, et al. Imatinib mesylate suppresses cytokine synthesis by activated CD4 T cells of patients with chronic myelogenous leukemia. Leukemia. Nov 2005;19(11):1905- 1911.
60. Mattiuzzi GN, Cortes JE, Talpaz M, et al. Development of Varicella-Zoster virus infection in patients with chronic myelogenous leukemia treated with imatinib mesylate. Clin Cancer Res. Mar 2003;9(3):976-980.
61. Aswald JM, Lipton JH, Aswald S, Messner HA. Increased IFN-gamma synthesis by T cells from patients on imatinib therapy for chronic myeloid leukemia. Cytokines Cell Mol Ther. 2002;7(4):143-149.
62. Bocchia M, Abruzzese E, Forconi F, et al. Imatinib does not impair specific antitumor T-cell immunity in patients with chronic myeloid leukemia. Leukemia. Jan 2006;20(1):142-143.
63. Bocchia M, Gentili S, Abruzzese E, et al. Effect of a p210 multipeptide vaccine associated with imatinib or interferon in patients with chronic myeloid leukaemia and persistent residual disease: a multicentre observational trial. Lancet. Feb 19-25 2005;365(9460):657-662.
64. Li Z, Qiao Y, Liu B, et al. Combination of imatinib mesylate with autologous leukocyte-derived heat shock protein and chronic myelogenous leukemia. Clin Cancer Res. Jun 15 2005;11(12):4460-4468.

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

65. Mohty M, Jourdan E, Mami NB, et al. Imatinib and plasmacytoid dendritic cell function in patients with chronic myeloid leukemia. Blood. Jun 15 2004;103(12):4666-4668.
66. Sato N, Narita M, Takahashi M, et al. The effects of STI571 on antigen presentation of dendritic cells generated from patients with chronic myelogenous leukemia. Hematol Oncol. Jun 2003;21(2):67-75.
67. Borg C, Terme M, Taieb J, et al. Novel mode of action of c-kit tyrosine kinase inhibitors leading to NK cell-dependent antitumor effects. J Clin Invest. Aug 2004;114(3):379-388.
68. Wang H, Cheng F, Cuenca A, et al. Imatinib mesylate (STI-571) enhances antigen-presenting cell function and overcomes tumor-induced CD4+ T-cell tolerance. Blood. Feb 1 2005;105(3):1135-1143.
69. Zeng Y, Graner MW, Feng H, Li G, Katsanis E. Imatinib mesylate effectively combines with chaperone-rich cell lysate-loaded dendritic cells to treat bcr-abl+ murine leukemia. Int J Cancer. Jun 10 2004;110(2):251-259.
70. Appel S, Boehmler AM, Grunebach F, et al. Imatinib mesylate affects the development and function of dendritic cells generated from CD34+ peripheral blood progenitor cells. Blood. Jan 15 2004;103(2):538-544.
71. Appel S, Rupf A, Weck MM, et al. Effects of imatinib on monocyte-derived dendritic cells are mediated by inhibition of nuclear factor-kappaB and Akt signaling pathways. Clin Cancer Res. Mar 1 2005;11(5):1928-1940.
72. Taieb J, Maruyama K, Borg C, Terme M, Zitvogel L. Imatinib mesylate impairs Flt3L-mediated dendritic cell expansion and antitumor effects in vivo. Blood. Mar 1 2004;103(5):1966-1967; author reply 1967.
73. Dewar AL, Cambareri AC, Zannettino AC, et al. Macrophage colony-stimulating factor receptor c-fms is a novel target of imatinib. Blood. Apr 15 2005;105(8):3127-3132.
74. Dewar AL, Doherty KV, Hughes TP, Lyons AB. Imatinib inhibits the functional capacity of cultured human monocytes. Immunol Cell Biol. Feb 2005;83(1):48-56.
75. Dewar AL, Domaschenz RM, Doherty KV, Hughes TP, Lyons AB. Imatinib inhibits the in vitro development of the monocyte/macrophage lineage from normal human bone marrow progenitors. Leukemia. Sep 2003;17(9):1713-1721.
76. Wolf AM, Wolf D, Rumpold H, et al. The kinase inhibitor imatinib mesylate inhibits TNF- {alpha} production in vitro and prevents TNF-dependent acute hepatic inflammation. Proc Natl Acad Sci U S A. Sep 20 2005;102(38):13622-13627.
77. Dietz AB, Souan L, Knutson GJ, Bulur PA, Litzow MR, Vuk-Pavlovic S. Imatinib mesylate inhibits T-cell proliferation in vitro and delayed-type hypersensitivity in vivo. Blood. Aug 15 2004;104(4):1094-1099.
78. Ando W, Hashimoto J, Nampei A, et al. Imatinib mesylate inhibits osteoclastogenesis and joint destruction in rats with collagen-induced arthritis (CIA). J Bone Miner Metab. 2006;24(4):274- 282.
79. D'Aura Swanson C, Paniagua RT, Lindstrom TM, Robinson WH. Tyrosine kinases as targets for the treatment of rheumatoid arthritis. Nat Rev Rheumatol. Jun 2009;5(6):317-324.
80. Koyama K, Hatsushika K, Ando T, et al. Imatinib mesylate both prevents and treats the arthritis induced by type II collagen antibody in mice. Mod Rheumatol. 2007;17(4):306-310.
81. Kameda H, Ishigami H, Suzuki M, Abe T, Takeuchi T. Imatinib mesylate inhibits proliferation of rheumatoid synovial fibroblast-like cells and phosphorylation of Gab adapter proteins activated by platelet-derived growth factor. Clin Exp Immunol. May 2006;144(2):335-341.
82. Paniagua RT, Sharpe O, Ho PP, et al. Selective tyrosine kinase inhibition by imatinib mesylate for the treatment of autoimmune arthritis. J Clin Invest. Oct 2006;116(10):2633-2642.
83. Sandler C, Joutsiniemi S, Lindstedt KA, Juutilainen T, Kovanen PT, Eklund KK. Imatinib mesylate inhibits platelet derived growth factor stimulated proliferation of rheumatoid synovial fibroblasts. Biochem Biophys Res Commun. Aug 18 2006;347(1):31-35.
84. Juurikivi A, Sandler C, Lindstedt KA, et al. Inhibition of c-kit tyrosine kinase by imatinib mesylate induces apoptosis in mast cells in rheumatoid synovia: a potential approach to the treatment of arthritis. Ann Rheum Dis. Aug 2005;64(8):1126-1131.
85. Sadanaga A, Nakashima H, Masutani K, et al. Amelioration of autoimmune nephritis by imatinib in MRL/lpr mice. Arthritis Rheum. Dec 2005;52(12):3987-3996.
86. Zoja C, Corna D, Rottoli D, Zanchi C, Abbate M, Remuzzi G. Imatinib ameliorates renal disease and survival in murine lupus autoimmune disease. Kidney Int. Jul 2006;70(1):97-103.
87. Soria A, Cario-Andre M, Lepreux S, et al. The effect of imatinib (Glivec) on scleroderma and normal dermal fibroblasts: a preclinical study. Dermatology. 2008;216(2):109-117.
88. Distler JH, Jungel A, Huber LC, et al. Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. Arthritis Rheum. Jan 2007;56(1):311-322.
89. Lozano E, Segarra M, Garcia-Martinez A, Hernandez-Rodriguez J, Cid MC. Imatinib mesylate inhibits in vitro and ex vivo biological responses related to vascular occlusion in giant cell arteritis. Ann Rheum Dis. Nov 2008;67(11):1581-1588.
90. Kalsch A-I, Soboletzki M, Schmitt WH, et al. Imatinib mesylate, a new kid on the block for the treatment of anti-neutrophil cytoplasmic autoantibodies-associated vasculitis? Clin Exp Immunol. 2007;151:391-398.

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

91. Ames PR, Aye WW, Beatty C, O'Reilly D. Imatinib treatment of seropositive arthritis in a young woman with chronic myeloid leukemia. J Rheumatol. Aug 2008;35(8):1682.
92. Eklund KK, Joensuu H. Treatment of rheumatoid arthritis with imatinib mesylate: clinical improvement in three refractory cases. Ann Med. 2003;35(5):362-367.
93. Eklund KK, Lindstedt K, Sandler C, et al. Maintained efficacy of the tyrosine kinase inhibitor imatinib mesylate in a patient with rheumatoid arthritis. J Clin Rheumatol. Oct 2008;14(5):294- 296.
94. Miyachi K, Ihara A, Hankins RW, Murai R, Maehiro S, Miyashita H. Efficacy of imatinib mesylate (STI571) treatment for a patient with rheumatoid arthritis developing chronic myelogenous leukemia. Clin Rheumatol. Oct 2003;22(4-5):329-332.
95. Bibi Y, Gottlieb AB. A potential role for imatinib and other small molecule tyrosine kinase inhibitors in the treatment of systemic and localized sclerosis. J Am Acad Dermatol. Oct 2008;59(4):654-658.
96. Chung L, Fiorentino DF, Benbarak MJ, et al. Molecular framework for response to imatinib mesylate in systemic sclerosis. Arthritis Rheum. Feb 2009;60(2):584-591.
97. Sfikakis PP, Gorgoulis VG, Katsiari CG, Evangelou K, Kostopoulos C, Black CM. Imatinib for the treatment of refractory, diffuse systemic sclerosis. Rheumatology (Oxford). May 2008;47(5):735-737.
98. van Daele PL, Dik WA, Thio HB, et al. Is imatinib mesylate a promising drug in systemic sclerosis? Arthritis Rheum. Aug 2008;58(8):2549-2552.
99. Eklund KK, Remitz A, Kautiainen H, Reitamo S, Leirisalo-Repo M. Three months treatment of active spondyloarthritis with imatinib mesylate: an open-label pilot study with six patients. Rheumatology (Oxford). Dec 2006;45(12):1573-1575.
100. Hofmann SC, Technau K, Muller AM, Lubbert M, Bruckner-Tuderman L. Bullous pemphigoid associated with hypereosinophilic syndrome: simultaneous response to imatinib. J Am Acad Dermatol. May 2007;56(5 Suppl):S68-72.
101. Magro F, Costa C. Long-standing remission of Crohn's disease under imatinib therapy in a patient with Crohn's disease. Inflamm Bowel Dis. Nov 2006;12(11):1087-1089.
102. Miyagawa S, Fujimoto H, Ko S, Hirota S, Kitamura Y. Improvement of psoriasis during imatinib therapy in a patient with a metastatic gastrointestinal stromal tumour. Br J Dermatol. Aug 2002;147(2):406-407.
103. Cwynarski K, Laylor R, Macchiarulo E, et al. Imatinib inhibits the activation and proliferation of normal T lymphocytes in vitro. Leukemia. Aug 2004;18(8):1332-1339.
104. Seggewiss R, Lore K, Greiner E, et al. Imatinib inhibits T-cell receptor-mediated T-cell proliferation and activation in a dose-dependent manner. Blood. Mar 15 2005;105(6):2473-2479.
105. Gale EA, Bingley PJ, Emmett CL, Collier T. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. Lancet. Mar 20 2004;363(9413):925-931.
106. Leder C, Ortler S, Seggewiss R, Einsele H, Wiendl H. Modulation of T-effector function by imatinib at the level of cytokine secretion. Exp Hematol. Aug 2007;35(8):1266-1271.
107. Mumprecht S, Matter M, Pavelic V, Ochsenbein AF. Imatinib mesylate selectively impairs expansion of memory cytotoxic T cells without affecting the control of primary viral infections. Blood. Nov 15 2006;108(10):3406-3413.
108. Sinai P, Berg RE, Haynie JM, Egorin MJ, Ilaria RL, Jr., Forman J. Imatinib mesylate inhibits antigen-specific memory CD8 T cell responses in vivo. J Immunol. Feb 15 2007;178(4):2028- 2037.
109. Chen J, Schmitt A, Chen B, et al. Imatinib impairs CD8+ T lymphocytes specifically directed against the leukemia-associated antigen RHAMM/CD168 in vitro. Cancer Immunol Immunother. Jun 2007;56(6):849-861.
110. Hagerkvist R, Sandler S, Mokhtari D, Welsh N. Amelioration of diabetes by imatinib mesylate (Gleevec): role of beta-cell NF-kappaB activation and anti-apoptotic preconditioning. FASEB J. Feb 2007;21(2):618-628.
111. Hagerkvist R, Makeeva N, Elliman S, Welsh N. Imatinib mesylate (Gleevec) protects against streptozotocin-induced diabetes and islet cell death in vitro. Cell Biol Int. Dec 2006;30(12):1013-1017.
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.
113. Shoda LK, Young DL, Ramanujan S, et al. A comprehensive review of interventions in the NOD mouse and implications for translation. Immunity. Aug 2005;23(2):115-126.
114. Chatenoud L, Thervet E, Primo J, Bach JF. Anti-CD3 antibody induces long-term remission of overt autoimmunity in nonobese diabetic mice. Proc Natl Acad Sci U S A. Jan 4 1994;91(1):123- 127.
115. Simon G, Parker M, Ramiya V, et al. Murine antithymocyte globulin therapy alters disease progression in NOD mice by a time-dependent induction of immunoregulation. Diabetes. Feb 2008;57(2):405-414.
116. Deininger MW, Druker BJ. Specific targeted therapy of chronic myelogenous leukemia with imatinib. Pharmacol Rev. Sep 2003;55(3):401-423.
117. Templeton A, Brandle M, Cerny T, Gillessen S. Remission of diabetes while on sunitinib treatment for renal cell

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

carcinoma. Ann Oncol. Apr 2008;19(4):824-825.
118. Hagerkvist R, Jansson L, Welsh N. Imatinib mesylate improves insulin sensitivity and glucose disposal rates in rats fed a high-fat diet. Clin Science. 2008;114:65-71.
119. Han MS, Chung KW, Cheon HG, et al. Imatinib mesylate reduces endoplasmic reticulum stress and induces remission of diabetes in db/db mice. Diabetes. Feb 2009;58(2):329-336.
120. Ozcan U, Cao Q, Yilmaz E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science. Oct 15 2004;306(5695):457-461.
121. Han D, Lerner AG, Vande Walle L, et al. IRE1alpha kinase activation modes control alternate endoribonuclease outputs to determine divergent cell fates. Cell. Aug 7 2009;138(3):562-575.
122. Breccia M, Muscaritoli M, Alimena G. Reduction of glycosylated hemoglobin with stable insulin levels in a diabetic patient with chronic myeloid leukemia responsive to imatinib. Haematologica. Nov 2005;90 Suppl:ECR21.
123. Breccia M, Muscaritoli M, Aversa Z, Mandelli F, Alimena G. Imatinib mesylate may improve fasting blood glucose in diabetic Ph+ chronic myelogenous leukemia patients responsive to treatment. J Clin Oncol. Nov 15 2004;22(22):4653-4655.
124. Veneri D, Franchini M, Bonora E. Imatinib and regression of type 2 diabetes. N Engl J Med. Mar 10 2005;352(10):1049-1050.
125. Franceschino A, Tornaghi L, Benemacher V, Assouline S, Gambacorti-Passerini C. Alterations in creatine kinase, phosphate and lipid values in patients with chronic myeloid leukemia during treatment with imatinib. Haematologica. Feb 2008;93(2):317-318.
126. Fitter S, Vandyke K, Schultz CG, White D, Hughes TP, Zannettino AC. Plasma adiponectin levels are markedly elevated in imatinib-treated chronic myeloid leukemia (CML) patients: a mechanism for improved insulin sensitivity in type 2 diabetic CML patients? J Clin Endocrinol Metab. Aug 2010;95(8):3763-3767.
127. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol. Feb 1 2008;26(4):620- 625.
128. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol. Feb 1 2008;26(4):626-632.
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.
130. Guilhot F. Indications for imatinib mesylate therapy and clinical management. Oncologist. 2004;9(3):271-281.
131. Hochhaus A, Druker B, Sawyers C, et al. Favorable long-term follow-up results over 6 years for response, survival, and safety with imatinib mesylate therapy in chronic-phase chronic myeloid leukemia after failure of interferon-alpha treatment. Blood. Feb 1 2008;111(3):1039-1043.
132. Champagne MA, Capdeville R, Krailo M, et al. Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study. Blood. Nov 1 2004;104(9):2655-2660.
133. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol. Nov 1 2009;27(31):5175-5181.
134. Menon-Andersen D, Mondick JT, Jayaraman B, et al. Population pharmacokinetics of imatinib mesylate and its metabolite in children and young adults. Cancer Chemother Pharmacol. Jan 2009;63(2):229-238.
135. Millot F, Guilhot J, Nelken B, et al. Imatinib mesylate is effective in children with chronic myelogenous leukemia in late chronic and advanced phase and in relapse after stem cell transplantation. Leukemia. Feb 2006;20(2):187-192.
136. Cario-Andre M, Ardilouze L, Pain C, Gauthier Y, Mahon FX, Taieb A. Imatinib mesilate inhibits melanogenesis in vitro. Br J Dermatol. Aug 2006;155(2):493-494.
137. Cerchione C, Fabbricini R, Pane F, Luciano L. Vitiligo-like lesions in an adult patient treated with Imatinib mesylate. Leuk Res. Feb 19 2009.
138. Han H, Yu YY, Wang YH. Imatinib mesylate-induced repigmentation of vitiligo lesions in a patient with recurrent gastrointestinal stromal tumors. J Am Acad Dermatol. Nov 2008;59(5 Suppl):S80-83.
139. Kerkela R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med. Aug 2006;12(8):908-916.
140. Verweij J, Casali PG, Kotasek D, et al. Imatinib does not induce cardiac left ventricular failure in gastrointestinal stromal tumours patients: analysis of EORTC-ISG-AGITG study 62005. Eur J Cancer. Apr 2007;43(6):974-978.
141. Atallah E, Durand JB, Kantarjian H, Cortes J. Congestive heart failure is a rare event in patients receiving

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

imatinib therapy. Blood. Aug 15 2007;110(4):1233-1237.
142. Chintalgattu V, Ai D, Langley RR, et al. Cardiomyocyte PDGFR-beta signaling is an essential component of the mouse cardiac response to load-induced stress. J Clin Invest. Feb 1 2010;120(2):472-484.
143. Ali R, Ozkalemkas F, Kimya Y, et al. Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Arch Gynecol Obstet. Dec 13 2008.
144. Ali R, Ozkalemkas F, Ozcelik T, et al. Pregnancy under treatment of imatinib and successful labor in a patient with chronic myelogenous leukemia (CML). Outcome of discontinuation of imatinib therapy after achieving a molecular remission. Leuk Res. Aug 2005;29(8):971-973.
145. Ali R, Ozkalemkas F, Ozcelik T, Ozkocaman V, Ozkan A. Imatinib and pregnancy. J Clin Oncol. Aug 10 2006;24(23):3812-3813; author reply 3813.
146. Ault P, Kantarjian H, O'Brien S, et al. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol. Mar 1 2006;24(7):1204-1208.
147. Buyukbayrak EE, Ergen B, Karsidag YK, Kars B, Turan C, Argon D. Pregnancy complicated with chronic myelogeneous leukemia (CML) successfully treated with imatinib: a case report. Arch Gynecol Obstet. Aug 2008;278(2):161-163.
148. Dolai TK, Bhargava R, Mahapatra M, et al. Is imatinib safe during pregnancy? Leuk Res. Apr 2009;33(4):572-573.
149. Hensley ML, Ford JM. Imatinib treatment: specific issues related to safety, fertility, and pregnancy. Semin Hematol. Apr 2003;40(2 Suppl 2):21-25.
150. Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood. Jun 15 2008;111(12):5505-5508.
151. Skoumalova I, Vondrakova J, Rohon P, et al. Successful childbirth in a patient with chronic myelogenous leukemia treated with imatinib mesylate during early pregnancy. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. Jun 2008;152(1):121-123.
152. Berman E, Nicolaides M, Maki RG, et al. Altered bone and mineral metabolism in patients receiving imatinib mesylate. N Engl J Med. May 11 2006;354(19):2006-2013.
153. O'Sullivan S, Naot D, Callon K, et al. Imatinib promotes osteoblast differentiation by inhibiting PDGFR signaling and inhibits osteoclastogenesis by both direct and stromal cell-dependent mechanisms. J Bone Miner Res. Nov 2007;22(11):1679-1689.
154. Vandyke K, Dewar AL, Fitter S, et al. Imatinib mesylate causes growth plate closure in vivo. Leukemia. Jul 23 2009.
155. Kimoto T, Inoue M, Kawa K. Growth deceleration in a girl treated with imatinib. Int J Hematol. Mar 2009;89(2):251-252.
156. Mariani S, Giona F, Basciani S, Brama M, Gnessi L. Low bone density and decreased inhibinB/FSH ratio in a boy treated with imatinib during puberty. Lancet. Jul 12 2008;372(9633):111- 112.
157. Schmid H, Jaeger BA, Lohse J, Suttorp M. Longitudinal growth retardation in a prepuberal girl with chronic myeloid leukemia on long-term treatment with imatinib. Haematologica. Aug 2009;94(8):1177-1179.
158. Schultz K, Bowman W, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. Journal of Clinical Oncology. 2009;27(31):5175-5181.
159. Shima Y, Nozu K, Nozu Y, et al. Recurrent EIARF and PRES with severe renal hypouricemia by compound heterozygous SLC2A9 mutation. Pediatrics. Jun 2011;127(6):e1621-1625.
160. Suttorp M, Yaniv I, Schultz KR. Controversies in the treatment of CML in children and adolescents: TKIs versus BMT? Biol Blood Marrow Transplant. Jan 2011;17(1 Suppl):S115- 122.
161. Pollack IF, Jakacki R, Blaney s, et al. Phase I trial of imatinib in children withnewly diagnosed brainstem and recurrentmalignant gliomas: A Pediatric Brain TumorConsortium report1. NeuroOnc. 2007(April):145-160.
162. Pollack IF, Jakacki R, Blaney S, et al. Phase I trial of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas: A Pediatric Brain Tumor Consortium report. NeuroOnc. 2007(April):145-160.
163. Greulich W, Pyle S. Radiographic Atlas of Skeletal Development of the Hand and Wrist, 2nd edition. Stanford, CA: Stanford University Press; 1959.
164. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. DIAMOND Project Group. Diabet Med. Aug 2006;23(8):857-866.
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.
166. Zgibor JC, Songer TJ, Kelsey SF, Drash AL, Orchard TJ. Influence of health care providers on the development of diabetes complications: long-term follow-up from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Care. Sep 2002;25(9):1584-1590.

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw

167. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. Jama. May 15 2002;287(19):2563-2569.
168. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. Dec 22 2005;353(25):2643-2653.
169. Nathan DM, Lachin J, Cleary P, et al. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med. Jun 5 2003;348(23):2294-2303.
170. White NH, Sun W, Cleary PA, et al. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. Arch Ophthalmol. Dec 2008;126(12):1707-1715.
171. Montanya E, Fernandez-Castaner M, Soler J. Improved metabolic control preserved beta-cell function two years after diagnosis of insulin-dependent diabetes mellitus. Diabetes Metab. Sep 1997;23(4):314-319.
172. Herold KC, Hagopian W, Auger JA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med. May 30 2002;346(22):1692-1698.

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus). https://dx.doi.org/10.17504/protocols.io.bu8knzuw