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This is a submitted version of a paper published in *Expert opinion on investigational drugs*.

Citation for the published paper:

Welsh, N. (2012)

"Does the small tyrosine kinase inhibitor imatinib mesylate counteract diabetes by affecting pancreatic islet amyloidosis and fibrosis?"

Expert opinion on investigational drugs

URL: <http://dx.doi.org/10.1517/13543784.2012.724398>

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Does the small tyrosine kinase inhibitor Imatinib Mesylate counteract diabetes by affecting pancreatic islet amyloidosis and fibrosis?

Abstract

Introduction: The small tyrosine kinase inhibitor Imatinib Mesylate (Gleevec) protects against diabetes, but it is not known how.

Areas covered: It has been suggested that islet amyloid and fibrotic deposits promote beta-cell failure and death, leading to Type 2 diabetes. As Imatinib is known to possess anti-fibrotic/amyloid properties, in for example systemic sclerosis and mouse models for Alzheimer's disease, the present review will discuss the possibility that Imatinib acts, at least in part, by ameliorating islet hyalinization and its consequences in the pathogenesis of Type 2 diabetes.

Expert opinion: A better understanding of how Imatinib counteracts Type 2 diabetes will possibly help to clarify the pathogenic role of islet amyloid and fibrosis, and hopefully lead to improved treatment of the disease.

Keywords

Pancreatic beta-cells, Type 2 diabetes, fibrosis, amyloid, Imatinib mesylate, insulin, IAPP

1. Introduction

The drug Imatinib mesylate (Gleevec) is currently used as treatment of chronic myeloid leukemia, GIST and other malignancies, diseases caused by the Bcr-Abl oncogene, or other tyrosine kinase mutations. Imatinib is a 2-phenylaminopyrimidine-based ATP-competitive inhibitor of the Abl protein kinase, and was created using the structure of the ATP-binding site of the kinase. Imatinib binds to and stabilizes the inactive form of Bcr-Abl, which leads to annulation of the effects of the Bcr-Abl oncoprotein through the inhibition of Bcr-Abl autophosphorylation and substrate phosphorylation [1]. Imatinib is the first member of a new class of agents that act by specifically inhibiting a certain mutated enzyme that is characteristic of a particular cancer cell, rather than non-specifically inhibiting and killing all rapidly dividing cells, and it reached clinical practice showing a mild side effect profile more than 10 years ago. Interestingly, this drug has been observed to possess antidiabetic activities, both in humans and in animal models for Type 1 and Type 2 diabetes.

2.1 Known targets of Imatinib

First, Imatinib is known to inhibit tyrosine kinases of the ABL family (c-Abl (ABL1), Arg (ABL2), v-Abl, BCR-Abl). Under physiological conditions, c-Abl has been shown to participate in the control of cytoskeletal functions, such as migration, adhesion and cell structure, and cell cycle progression [2,3]. C-Abl also controls actin binding, bundling and remodeling, receptor endocytosis and autophagy [4]. However, when cells are exposed to different forms of stress, c-Abl becomes highly activated, which leads to cell cycle arrest and apoptosis [5-7]. In the context of genotoxic stress,

c-Abl activates the stress-activated protein kinases (JNK and p38 MAPK), the tumor suppressors p53 and p73 [8-11], and interacts with the anti-apoptotic factor NF-kappaB [12]. In response to nitric oxide and ER stress, c-Abl seems to promote cell death via interactions with mitochondria and the endoplasmic reticulum [12-15].

Second, Imatinib inhibits the PDGF receptors alpha and beta (PDGFRalpha/beta). PDGFR alpha and beta are expressed in many cell types and regulate cellular proliferation and differentiation in response to PDGF-AA, PDGF-BB, PDGF-CC and PDGF-DD stimulation [16]. The PDGFRs control not only embryonic development and tumor growth, but also the development of fibrosis synergistically with TGF-beta [16]. Moreover, it is known that PDGF signaling is enhanced in arteriosclerosis and diabetes, possibly via high glucose [17], low PPAR gamma, ApoE and adiponectin [18-21], and that the enhanced PDGF signaling results in not only arteriosclerosis, but also possibly worsened insulin resistance [22]. It has been observed that Imatinib protects against diabetes-associated arteriosclerosis [23], probably via PDGFR inhibition, and it is thus conceivable that Imatinib-mediated protection against insulin resistance and diabetes, at least in part, involves inhibition of this pathway.

Third, tyrosine kinase inhibitors such as Imatinib are known to inhibit the stem cell factor (SCF) receptor c-Kit. SCF is an important growth factor for mast cells, promoting their generation from CD34⁺ progenitor cells [24]. SCF controls also mast cell survival and release of pro-inflammatory cytokines and chemokines and induces eosinophil adhesion and activation. SCF is up-regulated in inflammatory conditions both *in vitro* and *in vivo*, in humans and mice [24]. This indicates that inhibition of the SCF/c-Kit pathway may curtail the inflammatory component of both Type 1 and Type 2 diabetes.

Fourth, it has recently been observed that Imatinib inhibits the collagen-induced discoidin domain receptor 1 and 2 (DDR1/2) [25]. DDR1 is an extracellular matrix receptor, which has been reported to convey signals pertinent to the immune system and inflammatory reactions [26]. Thus, inhibition of this signaling pathway might dampen diabetes-associated inflammation.

2.2 Diabetes Mellitus Type 1 and 2

Type 1 diabetes is an autoimmune disease in which dysfunction and death of insulin-producing beta-cells is thought to arise from direct contact with immune cells and from exposure to cytotoxic pro-inflammatory cytokines and other toxic substances [27]. Typically, wide spread beta-cell damage and death results in a severe lack of insulin and dramatic symptoms of diabetes. In Type 2 diabetes beta-cells are also dysfunctional and damaged, possibly in response to peripheral insulin resistance, hyperglycemia, hyperlipidemia and proinflammatory cytokines, leading to a relative lack of insulin [28]. However, in this case beta-cell damage is less pronounced and dramatic resulting in a more gradual and discrete onset of the disease. The molecular events leading to diabetes-associated beta-cell dysfunction and death appear very complex and may involve, for example, the activation of mitogen-activated protein kinases (MAPK), such as JNK and p38, in response to metabolic perturbations, inflammation, aging and oxidative stress [28]. In this context it has also been proposed that beta-cell dysfunction/failure is either initiated or potentiated by islet hyalinisation, i.e. islet fibrosis and/or deposits of islet amyloid [29].

2.3 Islet amyloid and Type 2 diabetes

Amyloid deposits are frequently observed in the islets of human type 2 diabetes patients [30]. This amyloid consists mainly of the islet amyloid polypeptide (IAPP), which has precipitated by forming beta-pleated sheet structures that stack up into long fibrils [31]. The 37 aminoacid long peptide IAPP is produced and co-released with insulin from beta-cells. IAPP is generated from pre-IAPP by proteolytic processing, and it may be that impaired processing of pre-IAPP to IAPP aggravates islet amyloid formation [32]. It is not entirely clear in human type 2 diabetes whether islet amyloid formation occurs secondary to beta-cell dysfunction and death, or whether islet dysfunction occurs as a consequence to enhanced IAPP production and precipitation. However, in vivo studies using transgenic mice expressing the human IAPP gene point to the possibility of a direct pathogenic role of islet amyloid in Type 2 diabetes [33]. It appears that human IAPP promotes beta-cell failure and that soluble human IAPP oligomers are more toxic to beta-cells than the long mature fibrils [34,35]. IAPP oligomers may directly damage the beta-cells by destabilizing the plasma membrane and/or promoting oxidative stress [36-37]. In addition, recent studies have indicated that IAPP oligomers kill or damage beta-cells via the FAS-pathway [38], JNK-activation [39] or by inhibition of the K(ATP) channel [40]. It has also been suggested that islet amyloid formation negatively affects pericyte function and islet microcirculation resulting in unfavorable consequences for islet function and survival [41]. Furthermore, it is also possible that hypersecretion of pre-IAPP/IAPP from beta-cells may activate adjacent islet macrophages leading to increased production of proinflammatory chemo/cytokines and islet inflammation [42], which will further provoke beta-cell dysfunction.

2.4 Islet fibrosis in Type 2 diabetes

The pancreases of Type 2 diabetes patients usually display increased pericapillary, intra- and peri-islet fibrosis consisting mainly of extracellular matrix proteins such as collagens and fibronectin [43,44]. Fibrosis is thought to result from enhanced TGF-beta and PDGF receptor signaling, renin-angiotensin system activation, cytokine signaling and stellate cell activation [29]. Islet fibrosis is also associated with increased production of reactive oxygen radicals (ROS), generated by the NAD(P)H oxidase enzyme complex, and advanced glycation end products (AGE), that result non-enzymatically from prolonged hyperglycemia [29]. Deposits of islet fibrotic products may not only occur secondarily to islet inflammation and beta-cell failure in Type 2 diabetes, but may also participate directly in the vicious cycle leading to loss of insulin production. Indeed, it can be envisaged that replacement of normal islet extracellular matrix components with fibrotic deposits will harm beta-cells considering that beta-cells require a direct interaction with a specific endothelial basal membrane for optimal insulin production [45]. In addition, findings from rodent models of human Type 2 diabetes, in which early signs of pericapillary fibrosis have been reported, indicate impaired islet blood flow and release of insulin granule content to the circulation [44]. Thus, it may be that pericapillary fibrosis acts as a barrier that prevents first phase insulin release, which, at least in part, could explain the impaired first phase insulin release observed in Type 2 diabetes patients [29].

2.5 Imatinib counteracts Diabetes Mellitus

It has recently been observed that patients suffering from both leukemia and Type 2 diabetes were cured from not only leukemia, but also diabetes, when treated with

Imatinib [46-48]. Although two subsequent studies found no effect of Imatinib on diabetes [49,50], other additional studies report anti-hyperglycemic/anti-diabetic effects of Imatinib or similar tyrosine kinase inhibitors in humans [51-57]. These clinical studies clearly demonstrate that although not all type 2 diabetes patients benefit from Imatinib therapy, there is a substantial proportion that responds, and some cases so dramatically that they become insulin-independent. An anti-diabetic action of Imatinib in Type 2 diabetes is further supported by a recent observation that Imatinib counteracts high-fat diet induced insulin resistance and hyperglycemia in rats [58]. Moreover, in a study from 2009, Imatinib was also observed to induce remission of diabetes in *db/db* mice, possibly via decreasing ER stress and insulin resistance, and by increasing the beta-cell mass [59]. Also, Imatinib has been demonstrated to counteract streptozotocin-induced diabetes in rats [60]. It may be that Imatinib counteracts diabetes or diabetes-induced complications by affecting glucosaminoglycan synthesis and lipid deposition (61), Rho-activation and myocyte migration (62) and serum adiponectin levels (63). Thus, in both animal models and in Type 2 diabetes patients Imatinib seems to improve glycemic control, possibly via an insulin sensitizing effect.

Imatinib appears to prevent and reverse not only Type 2 diabetes, but also diabetes of animal models with a Type 1 diabetes resembling disease. Imatinib has been shown to protect against beta-cell death *in vitro*, via inhibition of *c-Abl*, and to prevent diabetes in NOD- and streptozotocin-diabetic mice, both models for human beta-cell destruction in Type 1 diabetes [64,65]. More recently, it has been observed that both Imatinib and Sunitinib not only prevented, but also reversed new-onset diabetes in NOD mice [66]. As Sunitinib inhibits the PDGF-receptor, but not *c-Abl*, it may be that

inhibition of the PDGF-receptor may play a more decisive role in the protection against diabetes in NOD mice than the inhibition of c-Abl. Nevertheless, there exists proof-of-principle in animal models for an anti-diabetic effect of Imatinib and similar tyrosine kinase inhibitors, and that a limited treatment period will not only reverse diabetes, but also mediate long-term protection against re-precipitation of the disease [66]. This has led investigators [67-69] to propose clinical trials in which Imatinib is given to new-onset Type 1 diabetes patients. Although different mechanisms of action have hitherto been proposed (Figure 1), the exact chain of events by which Imatinib counteracts both Type 1 and Type 2 diabetes are, however, not clear.

2.6 Imatinib and amyloidosis

Imatinib has been reported to exert certain anti-amyloidosis effects. First, it appears that Imatinib inhibits amyloid-beta formation in Alzheimer's disease by blocking the gamma-secretase activating protein [70]. A lowered activation of gamma-secretase results in less cleavage of the amyloid precursor protein carboxy-terminal fragment and less amyloid-beta formation. In addition, amyloid-beta seems to activate c-Abl-mediated Tau phosphorylation, an event that further stimulated progression of Alzheimer's disease and that is inhibited by Imatinib [71]. Thus, Imatinib may affect both the formation of amyloid-beta and the signaling events down-stream of amyloid-beta formation in Alzheimer's disease. Imatinib may also possess anti-amyloid properties in amyloid A amyloidosis. Amyloid A amyloidosis occurs as a result of chronic inflammatory reactions in diseases such as rheumatoid arthritis. In this case it is a fragment of the serum amyloid A (SAA) protein that forms amyloid deposits and production of this SAA fragment may, at least in part, require mast cell activity [72].

As inhibition of c-Kit on mast cells by Imatinib blocks mast cell activity [72], it has been speculated that Imatinib may ameliorate amyloid A amyloidosis in the context of the inflammatory disease rheumatoid arthritis.

2.7 Imatinib and fibrotic diseases

It is generally agreed that Imatinib, as judged by in vitro or animal studies, prevents the development of fibrosis [73]. Examples of fibrotic diseases in which Imatinib might have a beneficial effect are liver fibrosis, idiopathic pulmonary fibrosis and systemic sclerosis, and the mechanism by which Imatinib is thought to act is primarily by inhibition of the PDGF receptors. In fibrosis stellate- or other cells overproduce PDGF or autoantibodies that activate the PDGFR. This leads to the activation of fibroblasts that express the PDGF- α receptor, which will subsequently result in hyperproduction of extracellular matrix proteins and other pro-fibrotic mediators [73]. PDGFR signaling in fibrosis is further stimulated by the TGF- β pathway as systemic sclerosis fibroblasts are known to increase the expression of the PDGF- α receptor in response to TGF- β stimulation [74]. Interestingly, it has been reported that Imatinib counteracts not only the PDGF receptor, but also TGF- β signaling. It appears that c-Abl is activated by pro-fibrotic TGF- β signaling in a SMAD-independent manner [75]. This explains the antagonistic effects of Imatinib on TGF- β -induced fibrosis and on the cross talk between TGF- β and the PDGF receptor [75], Imatinib-induced reversal of pulmonary hypertension, via inhibition of PDGF receptor/TGF- β signaling, appears to occur by reduced proliferation and increased apoptosis of smooth muscle cells [75]. Fibrosis occurs not only in response to PDGR receptor and TGF- β , but also in response to cytokines such as IL-4, IL-10 and

IL-13 [76]. Imatinib has been reported to affect cytokine production in different situations [77], and was recently observed to decrease IL-4 producing CD4(+) T cells in patients with systemic sclerosis [78]. Thus, an Imatinib-induced blockage of the Th 2/IL-4 response may further promote a diminished fibrosis.

The promising anti-fibrotic activities of Imatinib observed in animal studies have, however, not been paralleled in human clinical trials. A number of trials dealing with systemic sclerosis and idiopathic pulmonary fibrosis have reported either none or only weak effects of Imatinib [73]. It has been suggested that the disappointing results of Imatinib therapy might have resulted from α_1 -acid glycoprotein-induced Imatinib inactivation. α_1 -acid glycoprotein is an acute phase serum protein that binds to and inactivates Imatinib, and it can be assumed that serum levels of this protein varies considerably among individuals so that patients with a more severe systemic inflammation/fibrosis exhibit higher levels of the protein [79]. In addition, the anti-fibrotic effects of Imatinib may also have been counteracted by Imatinib-induced pericyte dysfunction leading to microcirculatory disturbances [73]. Thus, it may be necessary to further refine Imatinib therapy so that adverse effects are avoided.

3. Conclusion - Putative anti-amyloid/fibrotic role of Imatinib in Type 2 diabetes

As discussed above, it may be that both islet fibrosis and amyloidosis contribute to beta-cell failure in Type 2 diabetes. It is also likely that Imatinib counteracts the pathological development of fibrosis, and possibly also some cases of amyloidosis. It is therefore possible to envisage a scenario in which the beneficial effects of Imatinib on Type 2 diabetes are, at least in part, a consequence of diminished islet fibrosis/amyloidosis. According to this hypothesis (Figure 2), episodes of insulin resistance-

driven hyperglycemia, hyperlipidemia, elevated levels of free fatty acids, and perhaps premature aging combined with specific genetic polymorphisms will cause beta-cells to hypersecrete both insulin and IAPP at both basal conditions and after a meal. This will stimulate islet macrophages and stellate cells to release proinflammatory cytokine/chemokines and other pro-fibrotic factors. The inflammatory factors released by the islet macrophages will augment islet ROS and AGE production, which will enhance the inappropriate production of pre-IAPP and extracellular matrix proteins, leading to an increased formation of toxic IAPP oligomers and early stages of fibrosis. Pericapillary fibrosis will hinder the release of secretory granule release to the blood stream and the IAPP oligomers will initiate beta-cell destruction leading to a gradual decrease in beta-cell mass. As beta-cells become more dysfunctional, the dynamic release of insulin is blunted, which will further augment peripheral insulin resistance and the vicious cycles leading to beta-cell failure and Type 2 diabetes. Assuming that Imatinib counteracts Type 2 diabetes by interfering with this chain of events, inhibition of PDGFR- and TGF-beta-induced fibrotic signaling, and inhibition of amyloid formation and amyloid-induced pro-apoptotic c-Abl signaling could partially block further deterioration of beta-cell function and survival. Further studies on the putative effects of Imatinib on islet fibrosis/amyloidosis might not only give us a better understanding on how Imatinib counteracts diabetes, but also improve our general conception on the pathogenesis of Type 2 diabetes.

4. Expert opinion

Throughout many years it has been frustratingly difficult to delineate the crucial events that lead to Type 2 diabetes. However, using the new drug Imatinib, which has

no similarity with traditional Type 2 diabetes drugs, and which has an anti-diabetic effect in humans, it may be that we have a tool for the unraveling of new insights pertinent to Type 2 diabetes. Imatinib is known to affect many processes, i.e. autoimmunity, inflammation, arteriosclerosis and apoptosis, and interference with each one of these events could result in improved metabolic control in diabetes. However, of particular interest may be that Imatinib counteracts fibrosis and in some cases also amyloidosis. Future studies that aim at determining whether Imatinib affects either production of amyloid/fibrosis, or the down-stream signaling events to islet hyalinization leading to beta-cell failure and death, could generate rewarding information. For example, does imatinib prevent islet hyalinization in islet transplantation to diabetic recipients? Or does Imatinib prevent hyalinization of human islets when cultured in vitro at different stressful conditions? Can Imatinib prevent hyalinization of islets of transgenic mice overexpressing hIAPP? Assuming that Imatinib protects against islet hyalinization, can knock-down of c-Abl, PDGFR or c-Kit mimic this effect? Finally, are there other small tyrosine kinase inhibitors that promote similar beneficial effects without adverse side-effects? Hopefully, some of these questions can be answered the next few years.

5. Article highlight box

1. Imatinib counteracts Type 2 diabetes in patient that also suffer from chronic myeloid leukemia.
2. Islet amyloid and islet fibrosis may actively participate in the development of beta-cell failure leading to Type 2 diabetes.

3. Imatinib possesses anti-fibrotic activities and may in some cases also ameliorate amyloidosis.
4. It is speculated that Imatinib, at least in part, may counteract diabetes by protecting against fibrosis and/or amyloid.
5. Further studies on Imatinib-induced effects of islet amyloid and/or fibrosis might help in understanding the pathogenesis of Type 2 diabetes.

Declaration of interest

This work was supported in part by the Swedish Research Council (2010-11564-15-3), the Swedish Diabetes Association, the family Ernfors Fund, Barndiabetesfonden, and the Novo-Nordisk Foundation. The author has no conflicts of interest that are relevant to the content of this article. Writing assistance was not utilized in the production of this manuscript.

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Figure 1

Selection of proposed mechanisms of action of Imatinib in Type 1 and Type 2 diabetes. Please see text for details.

Figure 2

Hypothetical model for the roles of islet amyloid, fibrosis and Imatinib in the pathogenesis of Type 2 diabetes. Please see text for details.