BRIEF REVIEW www.jasn.org

Imatinib: Novel Treatment of Immune-Mediated Kidney Injury

Eric Wallace* and Leslie Gewin*†

*Division of Nephrology, Department of Medicine, Vanderbilt University, Nashville, Tennessee, and †Department of Research, Veterans Affairs Hospital, Tennessee Valley Healthcare System, Nashville, Tennessee

ABSTRACT

The treatments for many autoimmune diseases are limited in efficacy, and long-term use is associated with severe adverse events. The tyrosine kinase inhibitors have proven to be well tolerated for long treatment periods, with minimal adverse events, in the oncology population. These agents have recently been used to treat autoimmune diseases. We review the potential mechanisms whereby tyrosine kinase inhibitors may modulate the immune response and inhibit fibrogenesis and discuss the current evidence for their use in the treatment of autoimmune diseases of the kidney.

J Am Soc Nephrol 24: 694–701, 2013. doi: 10.1681/ASN.2012080818

According to 2011 data from the U.S. Renal Data System, GN caused ESRD in 10% of prevalent dialysis patients and 6% of incident patients. Almost 10,000 incident dialysis patients from 2005 to 2009 carried the histologic diagnosis of membranous nephropathy, membranoproliferative GN type I, or lupus nephritis (LN).[1] In these inflammatory diseases, B cell–mediated antibody production, T cell proinflammatory cytokine production, macrophages, and dendritic cells all play a role in the pathogenesis of renal injury.[2,3] Inflammation plays an important physiologic role in response to injury, but prolonged infiltration of lymphocytes, macrophages, and dendritic cells also leads to fibrosis through increased generation of reactive oxygen species and production of profibrotic cytokines and growth factors. Many of the drugs currently used to treat autoimmune diseases of the kidney were originally developed as antineoplastic agents; they have suboptimal efficacy, and toxic adverse effects limit their use. A major advance in oncology has been the advent of tyrosine kinase inhibitors (TKIs). This class of medication is relatively well tolerated and has immunomodulating and antifibrotic properties that may render it a valuable tool in the treatment of autoimmune diseases of the kidney.

TKIS

The TKIs are widely used clinically for the treatment of such malignancies as chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs), and renal cell carcinoma. TKIs target protein tyrosine kinases (PTKs), which exist as transmembrane receptors or as intracellular nonreceptor PTK. Fifty-eight receptor PTKs and 32 cytoplasmic PTKs exist, and they differentially modulate important cellular effects.[4] Most TKIs act through competitive inhibition of the ATP binding site of the PTKs, thus blocking autophosphorylation and subsequent intracellular signal transduction, and their effects vary with type of PTK inhibition.[5]

Imatinib was the first TKI to be approved by the U.S. Food and Drug Administration for treatment of CML.[6] Imatinib blocks nonreceptor Abelson tyrosine kinase (c-abl) that is constitutively active in CML because of the BCR-ABL fusion oncogene. Imatinib's kinase inhibition is not specific for c-abl; it also blocks platelet-derived growth factor receptor (PDGFR), stem cell growth factor receptor (c-kit),[7] discoidin domain receptor (DDR) 1 and 2,[8] macrophage colony-stimulating factor receptor (c-fms),[9] and lymphocyte-associated kinase (lck).[10] Nilotinib is a TKI that inhibits the same PTK repertoire as imatinib but has an increased potency for c-abl inhibition. Although most of this review focuses on imatinib, nilotinib should exert similar effects.

Imatinib was originally designed for the treatment of CML, but its inhibitory effects on c-abl, c-kit, DDR, c-fms, and lck render it a potent immunomodulatory agent. Imatinib may also have antifibrotic properties both by modulating inflammation and by inhibiting PDGFR, DDR, and c-abl, a downstream mediator of TGF-β–dependent matrix production.[11] Imatinib's relatively safe adverse effect profile, coupled with its immune-modulating and antifibrotic effects, serves

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Eric Wallace, Paula Building 230, 728 Richard Arrington Boulevard, Birmingham, AL 35294. Email: ericlwallace@uab.edu

as a rationale for investigating this TKI as a potential therapeutic option for immune-mediated kidney diseases.[12] Despite promising results with the use of imatinib in murine models of kidney disease, only two case reports have described its use in human kidney disease.[13,14] This review summarizes the molecular mechanisms whereby imatinib alters the immune and fibrotic responses to injury, discusses the use of imatinib in animal models of renal injury, and reports the clinical data using imatinib to treat immune-mediated diseases of the kidney.

IMMUNOMODULATION BY IMATINIB

Imatinib has various immune modulating properties on B cells, T cells, dendritic cells, and macrophages, all of which play a role in the pathogenesis of chronic immune-mediated kidney disease. Through inhibition of c-kit, lck, c-abl, and c-fms, imatinib affects development of immune cell progenitors, immune cell activation, proliferation, and function (Figure 1). We describe the cell-specific effects of imatinib on key components of the immune system.

B Cells

Dysregulated antibody production by B cell lymphocytes is important in the pathogenesis of autoimmune diseases of the kidney. c-kit is important for B cell lymphopoiesis, as shown by c-kit–deficient mice, which have a significantly reduced number of pro–B cells as adults.[15] This effect is probably mediated through src kinase because mice that contain c-kit with a mutated src kinase docking site show a reduction in pro B cells similar to that of the c-kit null mouse.[16] Furthermore, treatment of normal adult mice with imatinib recapitulate this phenotype, suggesting that inhibition of c-kit with imatinib inhibits lymphopoiesis.[16] Imatinib's effects on B cell development could also be mediated by inhibition of c-abl because mice with a mutated c-abl demonstrated markedly diminished numbers of B cell precursors in both the bone marrow and spleen.[17] Thus, imatinib's inhibition of c-kit and c-abl may compromise normal B cell development in adults.

c-abl not only modulates B cell development but may also affect B cell activation. Consistent with this notion, B cells in c-abl null and mutant mice have reduced proliferation and activation in response to ligation of the B cell receptor (BCR).[18,19] Also, treatment of B cells from wild-type mice with imatinib inhibits the IgM-stimulated proliferation observed in untreated B cells.[20] C-abl promotes B cell activation by direct interaction with CD19, a transmembrane glycoprotein on the surface of immature and mature B cells, which acts as a co-receptor for BCR-mediated activation of B cells. Mice that underexpress or overexpress CD19 are hypoproliferative or hyperproliferative, respectively, in response to antigen.[21] CD19 colocalizes with c-abl *in vivo* and is directly phosphorylated by c-abl *in vitro*.[18] In addition, evidence suggests that c-abl plays a role in CD19-mediated B cell activation. C-abl null B cells stimulated by CD19 ligation show decreased release of intracellular calcium, a marker of B cell activation.[22] C-abl also promotes B cell activation and proliferation through phosphorylation of Bruton tyrosine kinase, an important mediator of BCR's downstream signaling. Although c-abl can phosphorylate Bruton tyrosine kinase *in vitro*, further studies are needed to determine its physiologic importance.[23]

Additional clinical data support imatinib's role as an inhibitor of B cell function, thus validating the preceding studies in murine models. Immunoprofiling of patients receiving imatinib for the treatment of CML and GIST reveals that imatinib

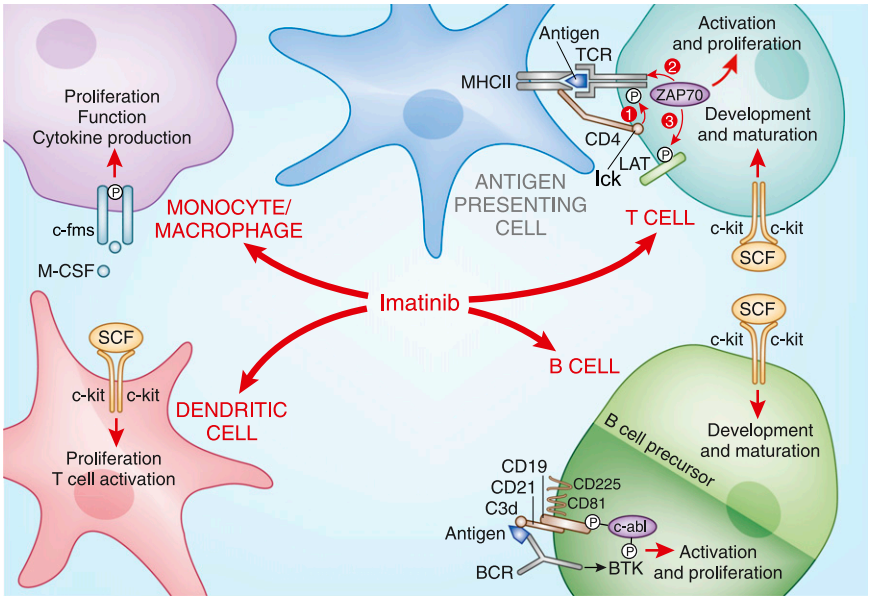

Figure 1. Imatinib's immunomodulatory effects. Red arrows indicate inhibition. B cell section: Inhibition of c-abl by imatinib prevents phosphorylation of Y490 of CD19, which in turn prevents downstream signaling of the signalosome (CD19, CD21, CD81, and CD225). Inhibition of c-abl phosphorylation of BTK also inhibits downstream signaling of BCR. These two actions inhibit B cell activation and proliferation in response to BCR stimulation by antigen. c-kit inhibition impairs B cell development and maturation. SCF, stem cell growth factor. T cell section: Imatinib directly inhibits lck, which phosphorylates the T cell receptor (TCR) (1). This leads to reduced recruitment of Zap70 (2) and subsequent decreased phosphorylation of linker for activation of T-cell (LAT) (3). The inhibition of this sequence of events decreases T cell activation, proliferation, and generation of cytokines. MHC, major histocompatibility complex. Monocyte/macrophage section: Imatinib inhibits c-fms, preventing proliferation, function, and production of such cytokines as IL-6 and TNF-α. Dendritic cell section: Dendritic cells treated with imatinib have reduced proliferation in response to stimulation with Flt3. In addition, imatinib-treated dendritic cells are unable to elicit a T cell response.

reduces levels of IgG, IgA, and IgM without an associated decrease in peripheral lymphocyte counts.[24,25] Imatinib reduced immunoglobulin levels in 69 of 72 patients with CML and 7 of 15 patients with GISTs, and immunoglobulin levels did not decrease in 20 patients with CML not treated with imatinib.[26] Furthermore, 21 of 30 patients with CML receiving treatment with imatinib demonstrate an abnormal plasma cell phenotype that correlates with decreased γ-globulin levels.[27] In summary, animal models suggest that imatinib affects the B cell immune response through decreased B cell development and function, and clinical studies suggest that imatinib dampens B cell production of antibodies.

T Cells

T cells can mediate renal injury in autoimmune disease by direct tissue injury and through secretion of cytokines that propagate inflammation.[2] Imatinib inhibits T cell development, activation, and proliferation through its inhibition of c-kit, c-abl, and lck. Signaling of c-kit is required for T cell lymphopoiesis, as illustrated by the adult c-kit null mice, which have a marked reduction in thymic T cell progenitor cells.[15] In addition, the ablm1 mouse, which contains a mutated src kinase docking site on c-abl, has a reduction in peripheral mature T cells as defined by single positivity for CD4 or CD8. The ablm1 mouse also has diminished T cell progenitor cells, and a similar phenotype is induced by imatinib treatment of wild-type adult mice.[16]

Imatinib also inhibits the activation and proliferation of healthy human donor peripheral T cells in response to stimulus.[10,28] One possible mechanism is through inhibition of lck, a PTK necessary for activation and proliferation of T cells.[29] Engagement of the T cell receptor activates lck, which then phosphorylates the intracytoplasmic portion of the T cell receptor; this, in turn, leads to downstream signaling events required for T cell activation and proliferation.[30] Among the downstream protein phosphorylation events inhibited by imatinib is linker for activation of T cells, whose deficiency causes profound T cell developmental defects.[31]

T cells secrete proinflammatory cytokines, such as IL-2, IFN-γ, and TNF-α, all of which have been implicated in autoimmune disease. IL-2 secretion has been used as a surrogate measure for downstream T cell receptor signaling, and imatinib inhibits this IL-2 secretion.[10] Imatinib has also been shown to inhibit production of TNF-α and of IFN-γ in T cells from both healthy donors and patients being treated for CML.[32,33] In summary, imatinib inhibits the T cell response by reducing lymphopoiesis through blockade of c-kit and c-abl and modulation of T cell function through lck, resulting in decreased activation, proliferation, and secretion of proinflammatory cytokines.

MONOCYTES, MACROPHAGES, AND DENDRITIC CELLS

Antigen-presenting cells, such as macrophages, monocytes, and dendritic cells, are an important component of the inflammatory response present in multiple models of kidney disease.[3,34] Macrophages propagate kidney injury through secretion of inflammatory cytokines, production of profibrotic growth factors, and generation of reactive oxygen species.[35–37] Macrophage depletion attenuated fibrosis in a unilateral ureteral obstruction (UUO) model of injury, suggesting that macrophage infiltration may be deleterious.[38] Imatinib-treated monocyte/macrophages *in vitro* had reduced proliferation in response to macrophage colony stimulating factor.[9] This finding was attributed to imatinib's inhibitory effect on the phosphorylation of c-fms, the receptor for macrophage colony-stimulating factor.[9] Inhibiting c-fms with a monoclonal antibody in mice reduces macrophage accumulation and proliferation in both the UUO and db/db diabetic models of injury.[39,40] Furthermore, the diabetic db/db mice treated with anti–c-fms have reduced tubular apoptosis and fibrosis, suggesting that macrophages are integral to the pathophysiology of this injury model. Imatinib also impairs the function of monocytes that differentiate into macrophages upon movement from the bloodstream to tissue. Human monocytes treated with imatinib *in vitro* had reduced phagocytosis, impaired formation of pseudopodia, and reduced production of proinflammatory cytokines (IL-6, TNF-α) in response to lipopolysaccharide.[41] Thus, imatinib treatment potentially modulates kidney injury through inhibition of monocyte-macrophage proliferation and function.

Dendritic cells, antigen-presenting cells that modulate T cell function, are also implicated in several murine models of GN.[42] Imatinib treatment inhibits the generation of dendritic cells from their CD34+ progenitors *in vitro*.[43] Similarly, administration of imatinib to mice attenuates the expansion of dendritic cells *in vivo* induced by Flt3L, a dendritic cell growth factor.[44] Furthermore, imatinib-treated dendritic cells are unable to induce primary T cell responses, suggesting that imatinib suppresses both dendritic cell expansion and function.[43]

ANTIFIBROTIC EFFECTS OF IMATINIB

Progressive fibrosis characterized by extracellular matrix (ECM) accumulation is the common pathway from injury of any cause to ESRD.[45] Imatinib not only has the potential to reduce fibrosis indirectly through decreased inflammation but also may directly inhibit fibrogenesis by modulating TGF-β, PDGFR, and DDR signaling (Figure 2).

TGF-β Signaling

TGF-β is a pleiotropic growth factor with strong profibrotic effects in models of renal injury.[46] TGF-β probably promotes fibrosis by stimulating fibroblast proliferation, activation, and production of ECM components as well as by inhibiting ECM degradation. TGF-β ligands bind to serine/threonine kinase receptors that signal through a canonical Smad-dependent pathway. However, many Smad-independent pathways contribute to TGF-β–mediated fibrosis, and c-abl

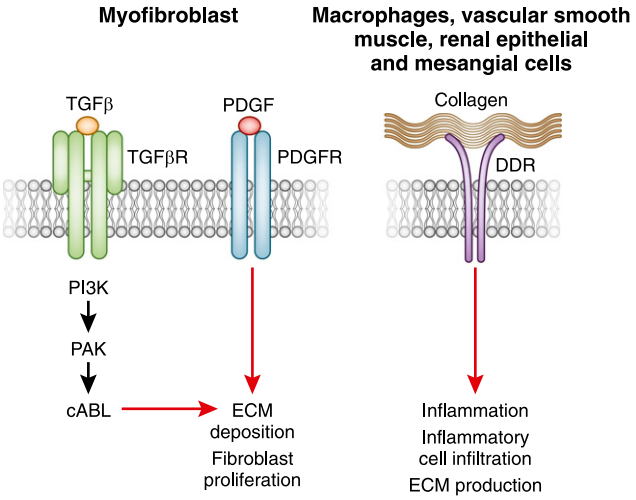

Figure 2. Fibrogenic pathways targeted by imatinib. TGF-β inhibition of c-abl inhibits a non–Smad-dependent TGF-β pathway and reduces fibrosis. This is a cell specific for mesenchymal cells. PI3K, phosphoinositide 3 kinase; PAK, p21 activated kinase. Imatinib inhibits PDGFR, thereby reducing ECM production and fibroblast proliferation DDR is the first tyrosine kinase to be shown to bind ECM. Inhibition of DDR through imatinib may result in decreased inflammation and ECM production, as demonstrated in a DDR null mouse.

also mediates TGF-β–dependent proliferation of renal fibroblasts *in vitro*.[11] This c-abl pathway is upregulated in a UUO model of renal injury, and treatment of these injured mice with imatinib reduces renal fibroblast proliferation and accumulation of ECM.[11,47] Thus, imatinib may prevent fibrosis through inhibition of noncanonical TGF-β signaling through c-abl. Because TGF-β activates c-abl in renal fibroblasts but not in renal tubular epithelial cells or mesangial cells, this pathway's cell specificity may render it an attractive pharmacologic target.[11]

PDGFR

PDGF, a known mitogen for mesenchymal cells, can stimulate ECM production in mesenchymal and parietal epithelial cells *in vitro*.[48] The four isoforms of PDGF (A, B, C, and D) signal through the tyrosine kinase receptor PDGFR, which exists as a dimer composed of α and β chains.[48] PDGF and its receptors are upregulated in numerous murine injury models and in human kidney disease.[48] Inhibition of PDGF signaling through neutralizing antibodies, oligonucleotides, and chemical antagonists can reduce mesenchymal cell proliferation and ECM accumulation.[48] Imatinib also blocks PDGF signaling and inhibits PDGF-induced mesangial proliferation *in vitro*.[49] In addition, a murine model of diabetes (streptozotocin-treated apoE knockout mice) showed attenuated collagen type I and IV production when given imatinib, a finding associated with reduced expression of PDGF, PDGFR and TGF-β1.[50] Thus, imatinib's inhibition of PDGFR signaling is another potential mechanism whereby imatinib reduces fibrosis.

DDR

There are two discoidin domain receptors, DDR1 and DDR2, both of which have tyrosine kinase activity and bind collagens.[8] In the kidney, DDRs are widely expressed in cells such as epithelia, fibroblasts, vascular smooth muscle cells, and mesangial cells.[50] DDRs are potent mediators of inflammation and fibrosis, and DDR1 null mice have reduced collagen accumulation and infiltrating inflammatory cells in both angiotensin II–induced renal injury and the UUO model of fibrosis.[51,52] DDR1 null mice are also protected from lipopolysaccharide-induced shock, confirming its pivotal role as a mediator of inflammation.[51] Imatinib inhibits DDRs *in vitro*, and this effect probably plays a role in imatinib's attenuation of fibrosis and inflammation observed in murine models of kidney disease.[8]

IMATINIB IN MURINE MODELS OF KIDNEY DISEASE

Through all of the preceding mechanisms, imatinib is a potential therapeutic agent for autoimmune mediated kidney disease. Imatinib has been investigated in various murine models of kidney disease and has been shown to improve both immunologic and fibrotic measures (Table 1).

Imatinib's inhibitory effect on B cells was illustrated in two models of murine LN and a mouse model of cryoglobulinemia.[53–55] In the two LN models, imatinib reduced anti–double-stranded DNA levels and decreased immune complex deposition.[53,54] This resulted in improved survival, creatinine, and proteinuria.[53,54] Cryoglobulinemia is another autoimmune disease caused by pathologic antibody secretion. A transgenic mouse model with constitutively active thymic stromal lymphopoietin resulted in cryoglobulin production and renal histologic lesions consistent with membranoproliferative GN caused by cryoglobulinemia.[55] Imatinib treatment in this mouse model reduces the cryocrit, serum levels of all immunoglobulins, mature and immature B cells, systemic manifestations of the disease, and C3 glomerular deposition. To highlight the immunomodulatory role of imatinib, the same thymic stromal lymphopoietin *tg* mouse model was treated with angiotensin-converting enzyme inhibition or angiotensin-receptor blocker therapy alone and showed no improvement in markers of immunologic activation.[56] Imatinib also inhibited T cell infiltration in mouse models of anti–glomerular basement membrane (GBM) disease and chronic allograft nephropathy.[57,58] Macrophage infiltration was decreased in models of chronic allograft nephropathy, streptozotocin-induced diabetic nephropathy, LN, and anti-GBM disease treated with imatinib whereas nilotinib

Table 1. Murine models of kidney disease treated with imatinib/nilotinib

Model of Kidney Disease	Intervention	Immune Effect	Effect on Fibrosis	Other Effects	Reference
Anti Thy 1.1 GN	Imatinib		↓Type IV collagen ↓αSMA	↓Mesangial cell activation and proliferation	49
Dark Agouti to Wistar Furth kidney transplant: CAN	Imatinib Short-term and long-term administration of imatinib	↓T cell and macrophage infiltration	↓CADI score ↓TGF-β and TGF-β receptor ↓PDGF-A and -B ↓PDGFR-α and -β	↓Creatinine	58,60,61
ApoE knockout/ Streptozotocin: diabetes	Imatinib	↓Macrophage infiltration	↓Tubulointerstitial fibrosis ↓ECM ↓PDGF-B, PDGFR-β, TGF-β ↓αSMA	↓Albuminuria ↓Glomerular size	50
TSLP transgenic mouse: cryoglobulinemia	Imatinib	↑Macrophage infiltration ↓Mature and Immature splenic B cells ↓Cryocrit and IgG, IgM ↓IC deposition ↓C3, IgG, IgM deposition Treatment with imatinib *in vivo* did not affect B cell proliferation in response to stimulation	↓ECM ↓ αSMA	↓Albuminuria ↓Liver and lung inflammatory cell infiltration	55
5/6 nephrectomized rats: CKD	Nilotinib	↓Macrophage infiltration ↓IL-6, IFN-ϒ, IL-1β, TNF-α, and MCP-1	↓Glomerular sclerosis ↓Collagen type I and IV, PAI1, fibronectin, PDGF-B, TGF-β	↓Creatinine ↓Proteinuria ↑Survival	59
Unilateral ureteral obstruction: renal fibrosis	Imatinib	No decrease in macrophage infiltration	↓Fibroblast proliferation ↓αSMA ↓ECM No decrease in PDGF-B		11
NZ black/white mouse: LN	Imatinib	Slightly diminished anti–double-stranded DNA ↓IC deposition ↓ Monocyte/macrophage infiltration	↓Interstitial fibrosis ↓αSMA ↓TGF-β	↑Survival ↓Creatinine ↓Proteinuria	53
MRL/*lpr* mouse: LN	Imatinib	↓Inflammatory cell infiltration ↓IgG and anti–double-stranded DNA ↓IFN-γ ↓IgG deposits	↓PDGFR-β, TGF-β	↑Survival ↓Creatinine ↓Proteinuria	54
Wistar-Kyoto rats: Anti-GBM	Imatinib	↓CD8+ but not CD3, CD4 ↓Crescent and fibrinoid necrosis ↓Macrophage infiltration ↓Proinflammatory cytokines ↓c-fms No difference in IgG deposition or levels	↓PDGFR-β	↓Proteinuria ↓BUN ↓Creatinine	57

CAN, chronic allograft nephropathy; CADI, chronic allograft damage index; apoE, apolipoprotein E; SMA, smooth muscle actin; TSLP, thymic stromal lymphopoietin; NZ, New Zealand; IC, immune complex; MCP, monocyte chemotactic protein; PAI1, plasminogen activator inhibitor 1.

Table 2. Current studies with imatinib/nilotinib/dasatinib in human autoimmune and fibrotic diseases

Study	Investigator/ Reference	Patient Population	Drug	Patients (*n*)	Completion Date	Endpoint	Results
NCT00555581	Spiera *et al.*[65]	Systemic sclerosis	Imatinib	30	1/2011	MRSS PFT results	Improved MRSS and PFT results
NCT01166139	Spiera	Systemic sclerosis	Nilotinib	10	Recruiting	MRSS PFT results	NA
NCT00154336	Novartis	Rheumatoid arthritis	Imatinib Methotrexate	54	Completed	ACR20	Not publicly available
NCT00131274	Daniels *et al.*[67]	Idiopathic pulmonary fibrosis	Imatinib	119	8/2007	Time to 10% decline in FVC and time to death	No improvement

MRSS, Modified Rodnan Skin Score; PFT, pulmonary function test; ACR20, 20% improvement in symptoms of rheumatoid arthritis per American College of Rheumatology criteria; FVC, forced vital capacity.

decreased macrophage infiltration in the 5/6 nephrectomy nephron reduction model.[50,53,54,57–59] Inflammatory cytokines were decreased by imatinib treatment in the models of anti-GBM and LN and by nilotinib treatment in the 5/6 nephrectomy model.[54,57,59] These findings provide further evidence for the immunomodulatory properties of imatinib and nilotinib.

Imatinib also markedly reduced ECM deposition and fibrosis in most of these murine models of kidney disease.[11,49,50,53,55,58–61] PDGF signaling was disrupted by imatinib, as shown by decreased levels of PDGF-A,[58] PDGF-B,[50,58,59], and PDGFR-β.[50,54,57,58] Imatinib also decreased levels of TGF-β[50,53,54,58,59] and TGF-β type I receptor[58] as well. Therefore, imatinib reduces indices of fibrosis in murine injury models with associated suppression of TGF-β and PDGF signaling, suggesting that imatinib may have beneficial antifibrotic effects in additional to its immunomodulatory properties.

HUMAN AUTOIMMUNE DISEASES TREATED WITH IMATINIB

Few clinical trials have used imatinib to treat autoimmune diseases. Anecdotally, there has been some clinical success. Case reports document that patients receiving imatinib for CML noted significant improvement in Crohn disease for one patient[62] and in severe rheumatoid arthritis for three patients.[63] Imatinib improved cutaneous involvement in three cases of systemic sclerosis and has subsequently been shown to improve skin thickness scores and pulmonary function test results in a larger trial of 30 patients with scleroderma.[64,65] Imatinib treatment improved skin thickening and tethering for two patients with nephrogenic sclerosing fibrosis.[66] Notably, imatinib did not prove effective in the treatment of idiopathic pulmonary fibrosis.[67]

As for kidney disease, a patient with biopsy-proven membranoproliferative GN had improvement in proteinuria and creatinine after initiation of imatinib for concurrent CML.[14] Imatinib treatment also resulted in a dramatic improvement in a patient with idiopathic type II cryoglobulinemia with kidney involvement. The patient's creatinine level, symptoms, and cryocrit improved upon starting imatinib, worsened upon withdrawal of therapy, and dramatically improved with reinstitution of therapy.[13] Table 2 lists ongoing and completed trials using imatinib or nilotinib for fibrotic diseases and rheumatoid arthritis.

CONCLUSIONS

Imatinib and nilotinib have improved both fibrotic and inflammatory markers of many murine models of kidney disease and, anecdotally, two clinical cases of immune-mediated kidney disease. As discussed here, the putative mechanism whereby TKI may be effective therapeutically for autoimmune renal disease involves the inhibition of their many PTK targets: c-abl, c-kit, lck, c-fms, PDGFR, and DDR. Blockade of these targets may inhibit the immune response and suppress fibrosis, two vital effects for halting the progression of autoimmune kidney disease.

Furthermore, imatinib's mild adverse effect profile and long-term safety record, particularly in comparison with those of current treatment options for these diseases, make this drug a potentially attractive alternative pending further studies conducted specifically in patients with autoimmune diseases. Diseases likely to benefit most from this intervention would be those necessitating chronic suppression of antibody production, such as severe membranous nephropathy, systemic lupus erythematosus, chronic humoral rejection after renal transplantation, and cryoglobulinemic vasculitis. Given the current limitations of therapies for immune-mediated kidney diseases, clinical trials are desperately needed to determine whether imatinib provides a safer and more efficacious option.

ACKNOWLEDGMENTS

The authors would like to thank Gerald Schulman and Roy Zent for their mentorship and review of the manuscript. This work was supported by a Career Development Award from the Department of Veterans Affairs, Veterans Health Administration, Biomedical Laboratory Research and Development (L.G.). This material is the result of work supported with resources at the Veterans Affairs Tennessee Valley Healthcare System.

DISCLOSURES

None.

REFERENCES

1. U.S. Renal Data System: *UADRAoCKDaE-SRDitUS*. Available at: http://www.usrds.org/qtr/default.aspx. Accessed March 12, 2012
2. Couser WG: Basic and translational concepts of immune-mediated glomerular diseases. *J Am Soc Nephrol* 23: 381–399, 2012
3. Wang Y, Harris DC: Macrophages in renal disease. *J Am Soc Nephrol* 22: 21–27, 2011
4. Robinson DR, Wu YM, Lin SF: The protein tyrosine kinase family of the human genome. *Oncogene* 19: 5548–5557, 2000
5. Hartmann JT, Haap M, Kopp HG, Lipp HP: Tyrosine kinase inhibitors: A review on pharmacology, metabolism and side effects. *Curr Drug Metab* 10: 470–481, 2009
6. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers CL: Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 344: 1031–1037, 2001
7. Carroll M, Ohno-Jones S, Tamura S, Buchdunger E, Zimmermann J, Lydon NB, Gilliland DG, Druker BJ: CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins. *Blood* 90: 4947–4952, 1997
8. Day E, Waters B, Spiegel K, Alnadaf T, Manley PW, Buchdunger E, Walker C, Jarai G: Inhibition of collagen-induced discoidin domain receptor 1 and 2 activation by imatinib, nilotinib and dasatinib. *Eur J Pharmacol* 599: 44–53, 2008
9. Dewar AL, Cambareri AC, Zannettino AC, Miller BL, Doherty KV, Hughes TP, Lyons AB: Macrophage colony-stimulating factor receptor c-fms is a novel target of imatinib. *Blood* 105: 3127–3132, 2005
10. Seggewiss R, Loré K, Greiner E, Magnusson MK, Price DA, Douek DC, Dunbar CE, Wiestner A: Imatinib inhibits T-cell receptor-mediated T-cell proliferation and activation in a dose-dependent manner. *Blood* 105: 2473–2479, 2005
11. Wang S, Wilkes MC, Leof EB, Hirschberg R: Imatinib mesylate blocks a non-Smad TGF-beta pathway and reduces renal fibrogenesis in vivo. *FASEB J* 19: 1–11, 2005
12. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, Deininger MW, Silver RT, Goldman JM, Stone RM, Cervantes F, Hochhaus A, Powell BL, Gabrilove JL, Rousselot P, Reiffers J, Cornelissen JJ, Hughes T, Agis H, Fischer T, Verhoef G, Shepherd J, Saglio G, Gratwohl A, Nielsen JL, Radich JP, Simonsson B, Taylor K, Baccarani M, So C, Letvak L, Larson RA; IRIS Investigators: Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 355: 2408–2417, 2006
13. Wallace E, Fogo AB, Schulman G: Imatinib therapy for non-infection-related type II cryoglobulinemia with membranoproliferative glomerulonephritis. *Am J Kidney Dis* 59: 122–125, 2012
14. Dwyer JP, Yates KM, Sumner EL, Stone WJ, Wang Y, Koury MJ, Fogo AB, Zent R: Chronic myeloid leukemia-associated membranoproliferative glomerulonephritis that responded to imatinib mesylate therapy. *Clin Nephrol* 67: 176–181, 2007
15. Waskow C, Paul S, Haller C, Gassmann M, Rodewald HR: Viable c-Kit(W/W) mutants reveal pivotal role for c-kit in the maintenance of lymphopoiesis. *Immunity* 17: 277–288, 2002
16. Agosti V, Corbacioglu S, Ehlers I, Waskow C, Sommer G, Berrozpe G, Kissel H, Tucker CM, Manova K, Moore MA, Rodewald HR, Besmer P: Critical role for Kit-mediated Src kinase but not PI 3-kinase signaling in pro T and pro B cell development. *J Exp Med* 199: 867–878, 2004
17. Schwartzberg PL, Stall AM, Hardin JD, Bowdish KS, Humaran T, Boast S, Harbison ML, Robertson EJ, Goff SP: Mice homozygous for the ablm1 mutation show poor viability and depletion of selected B and T cell populations. *Cell* 65: 1165–1175, 1991
18. Zipfel PA, Grove M, Blackburn K, Fujimoto M, Tedder TF, Pendergast AM: The c-Abl tyrosine kinase is regulated downstream of the B cell antigen receptor and interacts with CD19. *J Immunol* 165: 6872–6879, 2000
19. Hardin JD, Boast S, Schwartzberg PL, Lee G, Alt FW, Stall AM, Goff SP: Abnormal peripheral lymphocyte function in c-abl mutant mice. *Cell Immunol* 172: 100–107, 1996
20. Paniagua RT, Sharpe O, Ho PP, Chan SM, Chang A, Higgins JP, Tomooka BH, Thomas FM, Song JJ, Goodman SB, Lee DM, Genovese MC, Utz PJ, Steinman L, Robinson WH: Selective tyrosine kinase inhibition by imatinib mesylate for the treatment of autoimmune arthritis. *J Clin Invest* 116: 2633–2642, 2006
21. Fujimoto M, Poe JC, Inaoki M, Tedder TF: CD19 regulates B lymphocyte responses to transmembrane signals. *Semin Immunol* 10: 267–277, 1998
22. Liberatore RA, Goff SP: c-Abl-deficient mice exhibit reduced numbers of peritoneal B-1 cells and defects in BCR-induced B cell activation. *Int Immunol* 21: 403–414, 2009
23. Bäckesjö CM, Vargas L, Superti-Furga G, Smith CI: Phosphorylation of Bruton's tyrosine kinase by c-Abl. *Biochem Biophys Res Commun* 299: 510–515, 2002
24. Steegmann JL, Moreno G, Aláez C, Osorio S, Granda A, de la Cámara R, Arranz E, Reino FG, Salvanés FR, Fernández-Rañada JM, Muñoz C: Chronic myeloid leukemia patients resistant to or intolerant of interferon alpha and subsequently treated with imatinib show reduced immunoglobulin levels and hypogammaglobulinemia. *Haematologica* 88: 762–768, 2003
25. Cervetti G, Carulli G, Galimberti S, Azzarà A, Cannizzo E, Buda G, Orciuolo E, Petrini M: Reduction of immunoglobulin levels during imatinib therapy of chronic myeloid leukemia. *Leuk Res* 32: 191–192, 2008
26. Santachiara R, Maffei R, Martinelli S, Arcari A, Piacentini F, Trabacchi E, Alfieri P, Ferrari A, Leonardi G, Luppi G, Longo G, Vallisa D, Marasca R, Torelli G: Development of hypogammaglobulinemia in patients treated with imatinib for chronic myeloid leukemia or gastrointestinal stromal tumor. *Haematologica* 93: 1252–1255, 2008
27. Carulli G, Cannizzo E, Ottaviano V, Cervetti G, Buda G, Galimberti S, Baratè C, Marini A, Petrini M: Abnormal phenotype of bone marrow plasma cells in patients with chronic myeloid leukemia undergoing therapy with Imatinib. *Leuk Res* 34: 1336–1339, 2010
28. Cwynarski K, Laylor R, Macchiarulo E, Goldman J, Lombardi G, Melo JV, Dazzi F: Imatinib inhibits the activation and proliferation of normal T lymphocytes in vitro. *Leukemia* 18: 1332–1339, 2004
29. 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* 104: 1094–1099, 2004
30. Pribila JT, Shimizu Y: Signal transduction events regulating integrin function and T cell migration: New functions and complexity. *Immunol Res* 27: 107–128, 2003
31. Zhang W, Sommers CL, Burshtyn DN, Stebbins CC, DeJarnette JB, Trible RP, Grinberg A, Tsay HC, Jacobs HM, Kessler CM, Long EO, Love PE, Samelson LE: Essential role of LAT in T cell development. *Immunity* 10: 323–332, 1999
32. Gao H, Lee BN, Talpaz M, Donato NJ, Cortes JE, Kantarjian HM, Reuben JM: Imatinib mesylate suppresses cytokine synthesis by activated CD4 T cells of patients with chronic myelogenous leukemia. *Leukemia* 19: 1905–1911, 2005
33. Gao H, Lee BN, Donato NJ, Talpaz M, Reuben JM: Imatinib (Gleevec, STI-571) suppresses cytokine production by normal T cells activated through T-cell receptor (TCR) signaling. *J Allergy Clin Immunol* 115: S221, 2005
34. Menke J, Iwata Y, Rabacal WA, Basu R, Stanley ER, Kelley VR: Distinct roles of CSF-1 isoforms in lupus nephritis. *J Am Soc Nephrol* 22: 1821–1833, 2011
35. Matsumoto K: Production of interleukin-1 in macrophage cultures from rats with nephrotoxic serum nephritis. *Int Arch Allergy Appl Immunol* 87: 435–438, 1988
36. Tipping PG, Leong TW, Holdsworth SR: Tumor necrosis factor production by glomerular macrophages in anti-glomerular basement

membrane glomerulonephritis in rabbits. *Lab Invest* 65: 272–279, 1991
37. Boyce NW, Tipping PG, Holdsworth SR: Glomerular macrophages produce reactive oxygen species in experimental glomerulonephritis. *Kidney Int* 35: 778–782, 1989
38. Nishida M, Okumura Y, Fujimoto S, Shiraishi I, Itoi T, Hamaoka K: Adoptive transfer of macrophages ameliorates renal fibrosis in mice. *Biochem Biophys Res Commun* 332: 11–16, 2005
39. Le Meur Y, Tesch GH, Hill PA, Mu W, Foti R, Nikolic-Paterson DJ, Atkins RC: Macrophage accumulation at a site of renal inflammation is dependent on the M-CSF/c-fms pathway. *J Leukoc Biol* 72: 530–537, 2002
40. Lim AK, Ma FY, Nikolic-Paterson DJ, Thomas MC, Hurst LA, Tesch GH: Antibody blockade of c-fms suppresses the progression of inflammation and injury in early diabetic nephropathy in obese db/db mice. *Diabetologia* 52: 1669–1679, 2009
41. Dewar AL, Doherty KV, Hughes TP, Lyons AB: Imatinib inhibits the functional capacity of cultured human monocytes. *Immunol Cell Biol* 83: 48–56, 2005
42. Mack M: Podocyte antigens, dendritic cells and T cells contribute to renal injury in newly developed mouse models of glomerulonephritis. *Nephrol Dial Transplant* 24**:** 2984–2986, 2009
43. Appel S, Boehmler AM, Grünebach F, Müller MR, Rupf A, Weck MM, Hartmann U, Reichardt VL, Kanz L, Brümmendorf TH, Brossart P: Imatinib mesylate affects the development and function of dendritic cells generated from CD34+ peripheral blood progenitor cells. *Blood* 103: 538–544, 2004
44. Taieb, J, Maruyama, K, Borg, C, Terme, M & Zitvogel, L: Imatinib mesylate impairs Flt3L-mediated dendritic cell expansion and antitumor effects in vivo. *Blood* 103**:** 1966–1967; author reply 1967, 2004
45. Zeisberg M, Neilson EG: Mechanisms of tubulointerstitial fibrosis. *J Am Soc Nephrol* 21: 1819–1834, 2010
46. Klahr S, Morrissey J: Obstructive nephropathy and renal fibrosis. *Am J Physiol Renal Physiol* 283: F861–F875, 2002
47. Wang S, Wilkes MC, Leof EB, Hirschberg R: Noncanonical TGF-beta pathways, mTORC1 and Abl, in renal interstitial fibrogenesis. *Am J Physiol Renal Physiol* 298: F142–F149, 2010
48. Floege J, Eitner F, Alpers CE: A new look at platelet-derived growth factor in renal disease. *J Am Soc Nephrol* 19: 12–23, 2008
49. Gilbert RE, Kelly DJ, McKay T, Chadban S, Hill PA, Cooper ME, Atkins RC, Nikolic-Paterson DJ: PDGF signal transduction inhibition ameliorates experimental mesangial proliferative glomerulonephritis. *Kidney Int* 59: 1324–1332, 2001
50. Lassila M, Jandeleit-Dahm K, Seah KK, Smith CM, Calkin AC, Allen TJ, Cooper ME: Imatinib attenuates diabetic nephropathy in apolipoprotein E-knockout mice. *J Am Soc Nephrol* 16: 363–373, 2005
51. Flamant M, Placier S, Rodenas A, Curat CA, Vogel WF, Chatziantoniou C, Dussaule JC: Discoidin domain receptor 1 null mice are protected against hypertension-induced renal disease. *J Am Soc Nephrol* 17: 3374–3381, 2006
52. Guerrot D, Kerroch M, Placier S, Vandermeersch S, Trivin C, Mael-Ainin M, Chatziantoniou C, Dussaule JC: Discoidin domain receptor 1 is a major mediator of inflammation and fibrosis in obstructive nephropathy. *Am J Pathol* 179: 83–91, 2011
53. 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* 70: 97–103, 2006
54. Sadanaga A, Nakashima H, Masutani K, Miyake K, Shimizu S, Igawa T, Sugiyama N, Niiro H, Hirakata H, Harada M: Amelioration of autoimmune nephritis by imatinib in MRL/lpr mice. *Arthritis Rheum* 52: 3987–3996, 2005
55. Iyoda M, Hudkins KL, Becker-Herman S, Wietecha TA, Banas MC, Guo S, Meyer-Bahlburg A, Kowalewska J, Liu G, Ziegler SF, Rawlings DJ, Alpers CE: Imatinib suppresses cryoglobulinemia and secondary membranoproliferative glomerulonephritis. *J Am Soc Nephrol* 20: 68–77, 2009
56. Guo S, Kowalewska J, Wietecha TA, Iyoda M, Wang L, Yi K, Spencer M, Banas M, Alexandrescu S, Hudkins KL, Alpers CE: Renin-angiotensin system blockade is renoprotective in immune complex-mediated glomerulonephritis. *J Am Soc Nephrol* 19: 1168–1176, 2008
57. Iyoda M, Shibata T, Kawaguchi M, Yamaoka T, Akizawa T: Preventive and therapeutic effects of imatinib in Wistar-Kyoto rats with anti-glomerular basement membrane glomerulonephritis. *Kidney Int* 75: 1060–1070, 2009
58. Savikko J, Rintala JM, Rintala SE, Koskinen PK, von Willebrand E: Early short-term imatinib treatment is sufficient to prevent the development of chronic allograft nephropathy. *Nephrol Dial Transplant* 26: 3026–3032, 2011
59. Iyoda M, Shibata T, Hirai Y, Kuno Y, Akizawa T: Nilotinib attenuates renal injury and prolongs survival in chronic kidney disease. *J Am Soc Nephrol* 22: 1486–1496, 2011
60. Savikko J, Rintala J, von Willebrand E: Early short-term platelet-derived growth factor inhibition prevents the development of chronic allograft nephropathy in experimental rat kidney transplantation. *Transplant Proc* 38: 3231–3232, 2006
61. Savikko J, Taskinen E, Von Willebrand E: Chronic allograft nephropathy is prevented by inhibition of platelet-derived growth factor receptor: Tyrosine kinase inhibitors as a potential therapy. *Transplantation* 75: 1147–1153, 2003
62. Magro F, Costa C: Long-standing remission of Crohn's disease under imatinib therapy in a patient with Crohn's disease. *Inflamm Bowel Dis* 12: 1087–1089, 2006
63. Pereira I, Fialho S, Castro G, Zimmermann A: Imatinib mesylate induces clinical remission in rheumatoid arthritis. *Joint Bone Spine* 77: 372–373, 2010
64. Tamaki Z, Asano Y, Hatano M, Yao A, Kawashima T, Tomita M, Kinugawa K, Nagai R, Sato S: Efficacy of low-dose imatinib mesylate for cutaneous involvement in systemic sclerosis: a preliminary report of three cases. *Mod Rheumatol* 22: 94–99, 2012
65. Spiera RF, Gordon JK, Mersten JN, Magro CM, Mehta M, Wildman HF, Kloiber S, Kirou KA, Lyman S, Crow MK: Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: Results of a 1-year, phase IIa, single-arm, open-label clinical trial. *Ann Rheum Dis* 70: 1003–1009, 2011
66. Kay J, High WA: Imatinib mesylate treatment of nephrogenic systemic fibrosis. *Arthritis Rheum* 58: 2543–2548, 2008
67. Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR; Imatinib-IPF Study Investigators: Imatinib treatment for idiopathic pulmonary fibrosis: Randomized placebo-controlled trial results. *Am J Respir Crit Care Med* 181: 604–610, 2010