Long- and short-term treatment with imatinib attenuates the development of chronic kidney disease in experimental anti-glomerular basement membrane nephritis

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ABSTRACT

Background. Imatinib is a selective tyrosine kinase inhibitor that can block platelet-derived growth factor (PDGF) receptor activity. Imatinib is also known as an anti-inflammatory agent. We examined the therapeutic effects of long- or short-term imatinib treatment in Wistar-Kyoto (WKY) rats with established anti-glomerular basement membrane (GBM) nephritis.

Methods. Nephrotoxic serum (NTS) nephritis was induced in WKY rats on day 0. Groups of animals were given either imatinib or vehicle daily by intraperitoneal injection, from day 7 to day 49 in the long-term treatment study, and from day 7 to 13 in the short-term treatment study; all rats were sacrificed at day 50.

Results. In long-term treatment, imatinib showed marked renoprotective effects; imatinib suppressed proteinuria, improved renal function, attenuated the development of glomerulosclerosis and tubulointerstitial injury and reduced the expression levels of collagen type I and transforming growth factor-beta (TGF-β) in renal cortex. The key finding of the present study was that short-term treatment with imatinib also significantly attenuated the development of renal injury until day 50, although the degree of renoprotection was slightly inferior to that of long-term treatment.

Conclusions. These results suggest that administration of imatinib is a promising strategy for limiting the progression of glomerulonephritis (GN) to end-stage renal failure. In particular, a short period of treatment at an early stage of GN is more beneficial in terms of cost-effectiveness and reduction of adverse effects in comparison to a continuous and long period of treatment.

INTRODUCTION

Crescentic glomerulonephritis (GN) is characterized clinically by rapid deterioration of renal function and histologically by mononuclear cell infiltration in the glomeruli and tubulointerstitium, glomerular cell proliferation, necrotizing glomerular lesions, crescent formation and eventual glomerulosclerosis. In Wistar-Kyoto (WKY) rats, rabbit anti-rat glomerular basement membrane (GBM) antiserum (nephrotoxic serum, NTS) induces severe proliferative and necrotizing GN with crescent formation resembling human crescentic GN. It has been considered that the cardinal pathological features of crescentic GN are mediated in large part by the infiltration of monocytes/macrophages and T cells [1, 2]. In addition, several studies have suggested that some types of growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β) and connective tissue growth factor, may at least in part contribute to the process of glomerular crescent formation [3–5]. The chronic phase of this experimental model of anti-GBM nephritis has also been used as a model to investigate the
effects of drugs on pathophysiological events in the progression to end-stage renal failure [6–8].

Imatinib (Gleevec®, Novartis Pharmaceuticals Co., Basel, Switzerland), a selective tyrosine kinase inhibitor that inhibits Bcr-Abl, c-Kit and PDGF receptors (PDGFRs), has been demonstrated to be highly active in patients with Philadelphia chromosome-positive chronic myeloid leukemia (CML) and acute lymphoblastic leukemia, as well as in patients with a gastrointestinal stromal tumor (GIST) [9]. The therapeutic benefit of imatinib in animal models of kidney diseases (e.g. mesangial proliferative GN [10], chronic allograft nephropathy [11], diabetic nephropathy [12], lupus nephritis [13, 14], unilateral obstructive nephropathy [15], cryoglobulin-associated membranoproliferative GN (MPGN) [16] and anti-glomerular basement nephritis [17]) has been reported. In aggregate, these studies have shown that the beneficial effects of imatinib therapy are the result of its inhibitory action on PDGFR, leading to a reduction of glomerular cell proliferation and extracellular matrix accumulation.

Recently, we found beneficial effects of imatinib on WKY rats with anti-GBM nephritis [17]. Imatinib had a potent inhibitory effect on glomerular macrophage accumulation, possibly via inhibition of macrophage colony-stimulating factor/c-fms signaling in this model of nephritis. In that study, we verified that imatinib had preventive and therapeutic effects in the relatively acute phase of GN. These results prompted us to test whether treatment with imatinib for a long period of time could attenuate established GN and prevent subsequent progression to renal dysfunction and fibrosis. Our goal was to be able to apply this agent to patients with chronic kidney disease (CKD) in the future. Also of interest is whether treatment with imatinib for a short period of time in the early phase of GN is sufficient to prevent progression to end-stage renal failure. In the clinical setting, patients with GN already have renal dysfunction and/or proteinuria when the treatment starts. Therefore, imatinib was administered to rats 1 week after the induction of nephritis, that is, after the rats had already developed established GN. We found that not only long-term, but also short-term treatment with imatinib significantly attenuated the progression of renal dysfunction and fibrosis, even after the establishment of GN.

MATERIALS AND METHODS

Nephrotoxic serum

NTS was prepared as described previously [18]. The activity and specificity of NTS were tested by indirect immunofluorescence microscopy of frozen sections of a normal rat kidney.

Experimental protocol

The experimental protocol for this study was reviewed and approved by the Animal Care Committee of Showa University in Tokyo. Seven-week-old, female WKY rats weighing 150 g were purchased from Charles River, Japan (Atsugi, Kanagawa, Japan) and used in all of the experiments. The animals were housed in the animal care facility of Showa University (25°C, 50% humidity, 12-h dark/light cycle) with free access to food and water. A total of 36 female WKY rats were injected intravenously with 20 mL of NTS on day 0. Six rats with NTS-N were sacrificed at day 7. Seven control WKY rats received an equal volume of saline; the rats were then sacrificed at day 50. Thirty-six WKY rats with NTS-N were given either imatinib (25 mg/kg) or vehicle daily by intraperitoneal injection, from day 7 to day 49 in the long-term treatment study and from day 7 to day 13 in the short-term treatment study. The rats were then sacrificed at day 50. The vehicle-treated groups received an equal volume of sterile water. Seven control WKY rats received an equal volume of saline; the rats were then sacrificed at day 50.

Proteinuria and creatinine determination

For the analysis of proteinuria, the rats were housed individually in metabolic cages for 24-h urine collection. Urine samples were collected on the day before sacrifice. Serum creatinine (Cr) and urinary Cr were measured by standard methods using an automatic analyzer (Hitachi 7170, Hitachi, Tokyo, Japan). The Cr clearance (Ccr) was calculated using a standard formula.
**Measurement of circulating anti-rabbit IgG antibody**

The level of circulating anti-rabbit IgG antibody in rats with NTS-N was measured by enzyme-linked immunosorbent assay (ELISA) according to the ELISA procedure as described earlier [17,18].

**Light microscopy study**

Tissues fixed in 2% paraformaldehyde/PBS were embedded in paraffin using routine protocols. Paraffin-embedded materials were sectioned at 4 μm for routine staining with Masson trichrome. Two-μm-thick sections were used for periodic-acid methenamine silver stains (silver). Glomerulosclerosis was assessed in 50 glomeruli on silver-stained sections under ×400 magnification using a semiquantitative score from 0 to 4 (0, no sclerosis; 1, sclerosis up to 25% of glomeruli; 2, sclerosis from 25 to 50% of glomeruli; 3, sclerosis from 50 to 75% of glomeruli and 4, sclerosis >75% of glomeruli), and the results were averaged. For evaluating tubulointerstitial damage, 15 fields for each section (Masson trichrome stain) were evaluated at ×200 magnification using WinROOF image processing software (Mitani Corp., Tokyo, Japan). The extent of tubulointerstitial damage was evaluated by counting the percentage of areas with tubular dilatation, interstitial infiltration and fibrosis per field of cortex. Scores from 0 to 5 were used (0, normal interstitium; (i) <10% of areas injured; (ii) 11–25% of areas injured; (iii) 26–50% of areas injured; (iv) 51 to 75% of areas injured and (v) >75% of areas injured), and the results were averaged. All histological analyses were performed by two investigators without knowledge of the origin of the slides, and the mean values were calculated.

**Immunofluorescence**

The tissues were snap-frozen in liquid nitrogen and cut into 4-μm-thick sections. The deposits of rabbit IgG, rat fibrin, and rat IgG in the kidney sections were evaluated by staining with fluorescein-isothiocyanate-conjugated goat anti-rabbit IgG, anti-rat fibrinogen (Cappel; Organon Teknika, Durham, North Carolina) and rabbit anti-rat IgG (Sigma-Aldrich, St Louis, Missouri) using the method earlier described [18].

**Immunohistochemistry**

The monoclonal antibodies used in this study were mouse anti-rat ED1 antibody (BMA Biomedicals, Augst, Switzerland) as a macrophage marker; and mouse anti-rat CD8 antibody (Clone number: X8, Antigenix America, Inc., Huntington Station, New York). Biotinylated rabbit antimouse IgG and peroxidase-conjugated streptavidin (LSAB 2 kit/HRP) were purchased from Dako (Glostrup, Denmark). Immunohistochemical staining for ED1 and CD8 was performed according to our previous protocols [17].

**Real-time reverse transcriptase polymerase chain reaction**

Gene expressions of rat collagen type I, TGF-β and glycer-aldehyde-3-phosphate dehydrogenase (GAPDH) were analyzed using real-time RT-PCR as earlier described [17].

**Homogenization of kidney tissues and measurement of TGF-β1 protein levels in kidney tissue homogenate**

Homogenization of kidney tissues (cortex) was performed using a TissueLyser (QIAGEN, Inc., Valencia, California) and measurement of TGF-β1 protein levels in a kidney tissue homogenate was performed using the TGF-β 1 ELISA kit (R&D Systems, Abingdon, Oxfordshire, UK) as earlier described [19].

**Statistical analysis**

Data were recorded as means ± SEM. The Mann–Whitney test was performed, and the values of P < 0.05 were considered statistically significant.

**RESULTS**

**The characterization of renal histology in WKY rats with NTS on day 7**

Renal histological examination of the WKY rats with NTS on day 7 revealed established crescentic GN. Figure 2a shows typical silver-stained sections of glomeruli on day 7 in this group of rats. The glomeruli showed prominent cellular crescents with fibrinoid necrosis. Immunostaining for ED1 on day 7 showed intense glomerular staining (Figure 2b). Figure 2c depicts infiltration of CD8+ cells in the glomeruli on day 7. Prominent glomerular fibrin deposition was observed, as shown in Figure 2d. Rabbit immunoglobulin G (IgG) and rat IgG were detected in a linear pattern along the glomerular capillaries (data not shown).

**Long- and short-term treatment with imatinib significantly reduced proteinuria in rats with progressive renal failure**

The experimental design is described in Figure 1. The WKY rats with NTS developed substantial proteinuria on day 7 (Figure 3). In the long-term treatment study, which was performed from day 7 to day 49, urinary protein excretion in the rats treated with imatinib was significantly decreased compared with the vehicle-treated rats at each time point (day 14, P < 0.05; day 21, P < 0.0001; day 28, P < 0.01; day 35, P < 0.01; day 42, P < 0.05; day 49, P < 0.001) (Figure 3). A short-term imatinib treatment, which was performed from day 7 to day 13, also significantly reduced the urinary protein level at each time point except day 28 (day 14, P < 0.05; day 21, P < 0.05; day 28, NS; day 35, P < 0.01; day 42, P < 0.05; day 49, P < 0.05) (Figure 3).
Long- and short-term treatment with imatinib significantly preserved renal function in rats with progressive renal failure

Long-term treatment with imatinib significantly improved creatinine clearance (Ccr) and serum creatinine (Cr) levels compared with the vehicle-treated rats on day 50 (Ccr: P < 0.05; Cr: P < 0.01, Table 1). In the short-term treatment study, Ccr and serum Cr levels in the imatinib-treated rats on day 50 were also significantly higher and lower, respectively, than in the vehicle-treated rats (Ccr: P < 0.05; Cr: P < 0.05, Table 1).

Long- and short-term treatment with imatinib significantly reduced renal kidney weight in rats with progressive renal failure

Neither long-term nor short-term treatment with imatinib affected body weight compared with vehicle treatment (Table 1). Long-term treatment with imatinib in the WKY-NTS rats on day 50 demonstrated a significant decrease in kidney weight compared with the vehicle-treated rats (P < 0.001, Table 1). Short-term treatment with imatinib also significantly decreased kidney weight in the WKY-NTS rats on day 50 compared with the vehicle-treated rats (P < 0.05, Table 1).

Imatinib treatment affected neither the process of heterologous antibody deposition nor the production of autologous antibody

There was no significant difference in rabbit IgG and rat IgG glomerular staining between the vehicle- and imatinib-treated rats with NTS on day 50 in both the long- and short-term treatment studies (data not shown). Furthermore, there was no significant difference in the levels of serum anti-rabbit IgG antibody between the vehicle- and imatinib-treated rats with NTS in both the long- and short-term treatment studies [optical density (OD) value, long-term treatment 1.18 ± 0.05 versus 0.93 ± 0.08, NS; short-term treatment 0.67 ± 0.06 versus 0.52 ± 0.06, NS, vehicle-treated rats with NTS versus imatinib-treated rats with NTS; Normal WKY rats: 0.16 ± 0.009]. These findings suggest that imatinib treatment does not significantly affect the process of either heterologous antibody deposition or autologous antibody production.

Effects of long- and short-term treatment with imatinib on renal histological findings in rats with progressive renal failure

Figure 4 shows the representative silver and Masson’s trichrome stainings of the kidneys from the study groups. Renal histological findings in the rats with NTS-N were characterized by hypertrophy, glomerulosclerosis, fibrous crescents and tubulointerstitial fibrosis. The semiquantitative analysis of the renal histological injury is presented in Table 2. The glomerulosclerosis scores in the vehicle-treated WKY rats with NTS-N were significantly reduced by long-term (P < 0.01) and short-term (P < 0.05) treatment with imatinib. Moderate-to-severe tubulointerstitial damage was seen in the rats with NTS-N. Imatinib treatment significantly improved the tubulointerstitial damage in the rats with NTS-N (long-term treatment group: P < 0.01; short-term treatment group: P < 0.05).

Effects of long- and short-term treatment with imatinib on profibrogenic genes and proteins in rats with progressive renal failure

The gene expression levels of collagen type I and TGF-β were much higher in the rats with NTS-N than in the controls, as assessed by real-time reverse transcriptase polymerase chain reaction (RT-PCR) (Figure 5). Imatinib treatment significantly decreased collagen type I gene expression in the
Table 1. Effects of imatinib on renal function, body weight and kidney weight by the study group

<table>
<thead>
<tr>
<th>Group</th>
<th>Ccr (mL/h)</th>
<th>Cr (mg/dL)</th>
<th>Body weight (g)</th>
<th>Kidney weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY-NTS (−) (N = 7) 50</td>
<td>101.46 ± 6.60</td>
<td>0.25 ± 0.01</td>
<td>215.88 ± 3.69</td>
<td>1.42 ± 0.03</td>
</tr>
<tr>
<td>WKY-NTS (+) (N = 6) 7</td>
<td>80.19 ± 3.20</td>
<td>0.33 ± 0.01</td>
<td>133.83 ± 0.87</td>
<td>1.63 ± 0.03</td>
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<tr>
<td>Long-term treatmenta 50</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WKY-vehicle (N = 8)</td>
<td>60.71 ± 4.14##</td>
<td>0.39 ± 0.01**</td>
<td>200.23 ± 4.61##</td>
<td>2.09 ± 0.04##</td>
</tr>
<tr>
<td>WKY-imatinib (N = 8)</td>
<td>75.89 ± 3.83*</td>
<td>0.28 ± 0.01**</td>
<td>204.61 ± 2.43</td>
<td>1.68 ± 0.03***</td>
</tr>
<tr>
<td>Short-term treatmentb 50</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>WKY-vehicle (N = 10)</td>
<td>59.94 ± 7.55#</td>
<td>0.40 ± 0.05##</td>
<td>198.15 ± 3.30#</td>
<td>1.91 ± 0.07##</td>
</tr>
<tr>
<td>WKY-imatinib (N = 10)</td>
<td>74.13 ± 7.85*</td>
<td>0.32 ± 0.02*</td>
<td>204.99 ± 3.31</td>
<td>1.75 ± 0.05*</td>
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</table>

Ccr, creatinine clearance; Cr, creatinine; WKY, Wistar-Kyoto rats; NTS, nephrotoxic serum.

Data are expressed as mean ± sem.

Mann–Whitney test: *P < 0.05, **P < 0.01, ***P < 0.001 versus NTS-N rats with the same duration of vehicle treatment.

aP < 0.001, ##P < 0.001 versus WKY-NTS (−).

The rats were treated with either vehicle or imatinib from day 7 to day 49; the rats were sacrificed at day 50.

bThe rats were treated with either vehicle or imatinib from day 7 to day 13, the rats were sacrificed at day 50.

**Figure 4:** Light microscopy findings in the study groups. Representative pictures stained with silver (a, c, e, g and i) and Masson trichrome (b, d, f, h and j) in a WKY-vehicle rat (a, b, c and f), a WKY-imatinib rat (c, d, g and h) in long-term (a–d) and short-term (e–h) treatment groups and a control WKY rat (i and j). Original magnifications, ×200 (a, c, e, g and i) and ×40 (b, d, f, h and j).
kidneys of the rats with NTS-N in both the long-term (P < 0.01) and short-term (P < 0.01) treatment groups. Similar results were obtained in TGF-β1 gene expression (long-term treatment group: P < 0.01; short-term treatment group: P < 0.05). For examination of the effect of imatinib on TGF-β1 protein synthesis in the rats with NTS-N, kidney tissue homogenate was measured using the TGF-β1 ELISA kit (Figure 6). The TGF-β1 level was significantly higher in the rats with NTS-N than in the control rats (P < 0.001). There was a 32% (P < 0.05) and an 18% (NS) reduction of TGF-β1 by imatinib treatment in the rats with NTS-N in the long- and short-term treatment groups, respectively (Figure 6).

**DISCUSSION**

The aim of this study was to investigate the beneficial long-term effects of imatinib during the progressive phase of renal injury in rats with anti-GBM nephritis, and more importantly, to determine whether short-term administration of imatinib in an early phase of GN could affect the subsequent evolution of progressive renal disease. Imatinib was administered to rats with anti-GBM nephritis starting at 7 days after induction of nephritis, when necrotizing crescentic GN was completely established. In the long-term treatment (from day 7 to day 49), imatinib showed marked renoprotective effects; imatinib suppressed proteinuria, improved renal function as evaluated by Cr and serum Cr levels, attenuated the development of glomerulosclerosis and tubulointerstitial injury and

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<th>Table 2. Morphological evaluation of glomerular sclerosis and tubulointerstitial damage at the end of study</th>
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<tr>
<td>Group</td>
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<tr>
<td>WKY-NTS(−) (N = 7) day 50</td>
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<tr>
<td><strong>Long-term treatment</strong> day 50</td>
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<tr>
<td>WKY-vehicle (N = 8)</td>
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<tr>
<td>WKY-imatinib (N = 8)</td>
</tr>
<tr>
<td><strong>Short-term treatment</strong> day 50</td>
</tr>
<tr>
<td>WKY-vehicle (N = 10)</td>
</tr>
<tr>
<td>WKY-imatinib (N = 10)</td>
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</table>

WKY, Wistar-Kyoto rats; NTS, nephrotoxic serum.
Data are expressed as mean ± sem.
Mann–Whitney test: *P < 0.05, **P < 0.01 versus NTS-N rats with the same duration of vehicle treatment.

The rats were treated with either vehicle or imatinib from day 7 to day 49; the rats were sacrificed at day 50.

The rats were treated with either vehicle or imatinib from day 7 to day 13, the rats were sacrificed at day 50.
reduced the expression of collagen type I and TGF-β in renal cortex. These results were consistent with the results of previous studies designed to examine the renoprotective effects of imatinib in a chronic stage of GN [12,13,16]. More importantly, the present study showed that a short-term treatment with imatinib at the relatively early stage (from day 7 to day 13) also significantly attenuated the subsequent progression to end-stage renal failure until day 50, although the degree of renoprotection was slightly inferior to that in long-term treatment.

The interventional studies that show beneficial effects of PDGF-B/PDGFR-β signal inhibition in preventing the progression of CKD have been limited so far [19–22]. Recently, we demonstrated that nilotinib, a second-generation selective tyrosine kinase inhibitor that demonstrates a 30-fold increase in activity against Bcr-Abl and a similar level of activity against PDGFRs when compared with imatinib, attenuated renal disease progression and prolonged survival in rats with remnant kidney [19]. In that study, we speculated that the inhibitory effect of nilotinib against PDGFR-β in glomerular mesangial cells and renal fibroblasts, which was confirmed in vitro, might potentially contribute to the observed attenuation of renal injury [19]. It has been reported that the transient PDGF-B or -D antagonism during the mesangiproliferative phase of progressive anti-Thy 1.1 GN prevented subsequent development of CKD [20, 21]. Besides these reports, the beneficial effect of short-term treatment with imatinib in the present study indicates a potential contribution of PDGF/PDGFR signal activation at the early stage of GN to the subsequent development of end-stage renal failure. Furthermore, Savikko et al. [23] recently reported that treatment with imatinib for the first 30 days was sufficient to prevent the development of chronic allograft nephropathy in rats. Savikko et al. [23] performed the renal morphological investigations at 90 days after transplantation, although these authors did not evaluate either the differences in therapeutic effectiveness between short- and long-term treatments or the therapeutic effect of imatinib if started when the nephropathy is well established. Taken together, these data provide strong evidence that signaling inhibition of PDGFRs is a major effect of imatinib in attenuating the progressive phase of renal injury in rats with anti-GBM nephritis, which has been used as a model of CKD [6–8]. However, PDGFRs signaling inhibition in which cells contributed in attenuating this model of GN is unclear.

There is no previous report evaluating the potential role of imatinib in protecting parietal epithelial cells (PECs) or podocytes. In crescentic GN, PECs as well as podocytes are the first cells to proliferate along the inner aspect of Bowman’s capsule and to form cellular crescents [24, 25]. Recently, Bollee et al. reported that heparin-binding epithelial growth factor-like growth factor (HB-EGF) deficiency, conditional targeting of the tyrosine kinase receptor for HB-EGF [EGF receptor (EGFR)] alleles in podocytes or pharmacological blockade of EGFR tyrosine kinase activity markedly attenuated crescentic GN in mice [26]. They also showed de novo induction of HB-EGF in podocytes from both mice and humans with crescentic GN. Similar to the HB-EGF/EGFR pathway, the PDGF/PDGFRs pathway in PECs and podocytes is likely to be involved in the development of crescentic GN. It has been reported that the PDGF receptor localizes to PECs [27] and the podocyte-specific overexpression of PDGF-D causes crescentic GN [28]. These observations suggest the possibility that the potent therapeutic effect of imatinib on experimental crescentic GN was mediated through its direct action on these cells. Thus, we hypothesize that the short-term treatment of imatinib at an early stage of crescentic GN was enough to protect PECs and/or podocytes to prevent subsequent CKD development. Further in vitro studies will be required to determine the precise mechanism by which imatinib attenuates crescentic GN.

The improvement of renal function and tubulointerstitial fibrosis could be explained as a result of protective effect of imatinib on glomerular damage. However, the direct effect of imatinib on tubular cells cannot be ignored. The potential role for PDGF-D/PDGFR-β signal activation in the progression of tubulointerstitial injury in unilateral ureteral obstruction (UUO) in mice and humans was reported by Taneda et al. [29]. On the other hand, recent evidence suggests that PDGF-C, which exerts its biologic activity via PDGFR-α, has a pivotal role in tubulointerstitial inflammation and fibrosis [30, 31]. Eitner et al. [30] reported that murine renal fibrosis induced by UUO was reduced by using a neutralizing anti-PDGF-C antiserum and by inducing renal fibrosis in PDGF-C−/− mice. Accordingly, a direct effect of imatinib, which can block both PDGFR-α and -β on tubular cells, is plausible in the present study. Furthermore, Wang et al. [15, 32] reported the effects of imatinib on tubulointerstitial fibrosis, in which imatinib effectively blocked c-Abl, which is a non-Smad TGF-β pathway, in the kidney affected by obstructive nephropathy. In relation to these reports, we reported that nilotinib, which has a stronger binding affinity to c-Abl than does imatinib, attenuated glomerular sclerosis as well as tubulointerstitial fibrosis in rats with remnant kidney [19]. Thus, it is likely that c-Abl, in addition to PDGFRs, may be another target by which imatinib attenuates renal fibrosis. However, it is currently unclear whether only c-Abl tyrosine kinase inhibition is capable of mediating significant antiﬁbrotic effects in kidney disease. Recent studies have demonstrated an additional action of imatinib in tubular injury, in which imatinib blocks albumin-induced epithelial-mesenchymal transition and endoplasmic reticulum stress via inhibition of reactive oxygen species and c-Src kinase [33]. Imatinib has also been reported to attenuate pericyte proliferation and fibrosis in obstructive and post-ischemic kidney via inhibition of PDGFRs, which are involved in pericyte-myofibroblast transition [34].

Torres and Leof [35] stated that a number of issues, such as the timing of intervention, nature of the underlying renal disease, safety and tolerability, need to be considered with respect to the clinical use of tyrosine kinase inhibitors in treating kidney disease. Recently, Wallace et al. [36] were the first to use imatinib clinically in treating kidney disease. These authors administered imatinib at a daily dose of 400 mg to successfully improve renal
function and cryocrit in type II cryoglobulinemia and MPGN. This regimen was based on the basic research that Iyoda et al. reported in 2009 [16]. So far, however, imatinib has not been applied toward any other kidney diseases, including crescentic GN. Therapeutic approaches for primary nephritis rely on steroids and immunosuppressant drugs, which are not fully specific and carry the risk of toxic side effects. In view of the ample evidence for the therapeutic effects of imatinib on experimental kidney diseases over the last decade, first reported by Gilbert et al. in 2001 [10], and its abundant clinical use in which less toxicity and better tolerance than conventional chemotherapy has been confirmed in patients with CML and GIST, administration of imatinib seems to be a promising strategy for treating GN and tubulointerstitial nephritis in the clinical setting. While some tyrosine kinase inhibitors, specifically those directed against the vascular endothelial growth factor (VEGF), such as sunitinib, sorafenib, and bevacizumab, have been linked with the development of hypertension and proteinuria, imatinib is generally well tolerated and causes few adverse effects [37].

In conclusion, our results suggest that imatinib could limit the progression of GN to end-stage renal failure even if used for only a short period at an early stage of GN. This may be beneficial in terms of cost-effectiveness and reduction of adverse effects in comparison to continuous and long periods of treatment.

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CONFLICT OF INTEREST STATEMENT

None declared.


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