Bezafibrate suppresses rat antiglomerular basement membrane crescentic glomerulonephritis

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Background. The immunoregulatory activity of ligands for peroxisome proliferator-activated receptors (PPARs) has been recently paid attention. The regulatory effect of bezafibrate (BZF), a ligand for PPARα, on glomerulonephritis was investigated using a rat anti-globular basement membrane (GBM) glomerulonephritis model.

Methods. The effect on development of anti-GBM glomerulonephritis was examined by treatment with BZF from day −7 to day 7 after intravenous injection of rabbit anti-GBM serum into Wistar Kyoto (WKY) rats. The therapeutic efficacy after onset of the glomerulonephritis was also checked by treatment with BZF from day 3 to 7. On day 7, the condition was evaluated histologically. The expression of a tissue injury molecule, macrophage metalloelastase (MME), was measured by Northern blot analysis. The suppressive effect on immune cells was assessed by proliferation assay with mitogen-stimulated rat spleen cells.

Results. Histopathologic changes induced by anti-GBM in rats treated with BZF (day −7 to day 7) were markedly suppressed in a dose-dependent fashion. Infiltration of ED-1+ macrophages in glomeruli, proteinuria, and mRNA expression of MME in kidneys were diminished in parallel with histologic improvement. Moreover, the disease activity was also attenuated even by the treatment after onset of the glomerulonephritis (day 3 to 7). The mitogen-induced proliferation of spleen cells was down-regulated at concentrations of BZF, which were equivalent to those in sera of BZF-treated rats.

Conclusion. BZF markedly suppresses the activity of rat anti-GBM crescentic glomerulonephritis. Fibrates might serve as a therapeutic option for crescentic glomerulonephritis.

The peroxisome proliferators-activated receptors (PPARs) are ligand-activated transcription factors and a member of the nuclear receptor superfamily [1]. There are three isoforms of PPAR including α, β, and γ, which are differentially expressed in types of cells and tissues [2, 3]. PPARs are activated after binding of ligands, form heterodimers with retinoid receptors and bind to PPAR response elements in the promoters of target genes, whose products are involved in lipid metabolism, glucose homeostasis, cell proliferation, and cell differentiation [2, 3]. Recently, anti-inflammatory action of PPARα has been highlighted [3–10]. Fibrates, which are known as synthetic PPARα ligands, are widely used as lipid-lowering drugs. With respect to their suppressive effects on inflammation, there are some studies using inflammatory models such as reactive amyloidosis in mice [11] and autoimmune myocarditis in rats [12]. On the other hand, there are various reports showing their regulatory mechanisms in kinds of immune systems in vitro [13, 14].

Antiglomerular basement membrane (GBM) glomerulonephritis characterized by crescent formation and necrotizing inflammation of glomerular capillary is the most severe form of glomerulonephritis. The glomerulonephritis induced by injection of rabbit anti-GBM serum in Wistar Kyoto (WKY) rats is a model of this disease. Until today, a number of critical factors, such as complements, proinflammatory cytokines, chemokines, intercellular adhesion molecule-1 (ICAM-1), CD8+ lymphocytes and macrophages/mo/Mo, for the development of the anti-GBM glomerulonephritis have been revealed [15–20]. The glomerular injury is completely suppressed by deletion of CD8+ lymphocytes [16], showing the crucial role of cellular components in this model. In addition, we have recently reported that macrophage metalloelastase (MME), which was produced by infiltrating Mo, was a potent factor for glomerular injury in this model [21]. In early phase of the glomerulonephritis, CD8+ lymphocytes appear in glomeruli, peaking 3 days after anti-GBM serum injection, and enhance the expression of adhesion molecules on glomerular endothelial cells by releasing.
proinflammatory cytokines and chemokines. Mø/Mo appear later and participate in developing crescentic glomerulonephritis [18, 20].

Here we report that a fibrate, bezafibrate (BZF), markedly suppresses the development of the crescentic glomerulonephritis model. Results reported in this study might suggest that BZF, which is being used worldwide for lowering lipids, could be applied for the treatment of crescentic glomerulonephritis.

METHODS

Experimental design and animals

Male WKY/NCrj rats (7 weeks old) were purchased from Charles River Japan (Yokohama, Japan). Animal care was performed in accordance with the guidelines of Niigata University. Rats were randomly divided into four groups. Each group included six rats. On day −7, two groups started to receive BZF (44, 133, or 400 mg/kg/day) by gavage, twice per day, and continued to receive BZF until end. BZF was kindly provided by Kiisei Pharmaceutical Co., Ltd. The dose of administration was determined by previous experiments using rodents [11, 22]. Another group received only vehicle (0.05% carboxymethyl cellulose) in a same fashion. The other group received neither (negative control). On day 0, rats in the three groups, except for the negative control, were injected intravenously with rabbit anti-GBM serum (200 μL, containing about 2 mg IgG), which was prepared as previously described [16, 19]. On day 6, rats were placed in metabolic cages for 24 hours for urine collection, and concentrations of total protein and creatinine in urine were measured. On day 7 after anti-GBM serum injection, 7 hours after the first administration of BZF in the day, rats were bled under anesthesia by diethyl ether inhalation and sacrificed after removal of kidneys. Renal tissues were snap frozen or fixed in 10% formalin. As for investigating the therapeutic effect of BZF on the glomerulonephritis after the disease induction, rats were divided into three groups. Treatment with either vehicle (N = 6) or BZF (400 mg/kg/day) (N = 6) was started from day 3 after anti-GBM serum injection and continued until end (day 7). The negative control group (N = 6) received neither anti-GBM serum injection nor BZF administration. Urine and kidney samples were collected by the same way as described above.

Histologic evaluation

Renal tissues fixed in 10% formalin, embedded in paraffin, were cut into 10 μm sections, and stained with periodic acid-Schiff (PAS) for histologic analysis. About 100 glomeruli were evaluated and the percentage of glomeruli accompanied by necrotizing glomerulitis or crescent formation was quantitated by two independent observers in a blind fashion.

Immunohistochemistry

For detection of rabbit Ig deposition in glomeruli, frozen sections of kidney tissues were quenched with 0.3% hydrogen peroxide and treated with goat antirabbit Ig-conjugated peroxidase-labeled polymer (Dako, Carpinteria, CA, USA) for 30 minutes. For detection of ED-1 or CD8, paraffin sections were quenched and incubated with mouse antirat ED-1 monoclonal antibody (Serotec, Oxford, UK) or mouse antirat CD8 (Cosmo Bio, Tokyo, Japan) monoclonal antibody for 60 minutes at room temperature, followed by goat antimouse Ig-conjugated peroxidase-labeled polymer (Dako). The calorimetric reaction was developed with 3,3′-diaminobenzidine tetrahydrochloride (DAB) (Dako) and counterstaining was performed with hematoxylin. Thirty glomeruli were evaluated and the number of ED-1+ or CD8+ cells in glomerulus was counted by two independent observers in a blind fashion.

Measurement of serum parameters

Values of creatinine, total cholesterol, and triglyceride were determined enzymatically. The concentration of BZF in serum was measured using high-performance liquid chromatography (HPLC) with a Tosoh ODS 80TM column [23].

Estimation of antirabbit Ig antibody levels in serum

Antirabbit Ig antibody titer in rat serum was determined by enzyme-linked immunosorbent assay (ELISA) as described previously [21]. Briefly, 1/100 diluted sera from rats were incubated on wells coated with normal rabbit IgG (500 ng) followed by blocking with 0.5% bovine serum albumin (BSA). After washing, wells were then incubated with 1/4000 diluted horseradish peroxidase (HRP)-conjugated goat antirat IgG + monoclonal antibody. The colorimetric reaction using tetramethylbenzidine product was quantified by measuring the absorbance at 450 nm. Normal rat serum and serum from the rat immunized with rabbit Ig were used as a negative and a positive control, respectively.

Northern blot analysis

Total RNA was isolated from whole kidneys of each experimental groups using RNA extraction solution (Isogen, Nippon Gene, Tokyo, Japan). Total RNA was loaded on 1.5% agarose gel, transferred onto nylon membrane (Hi-bond N) (Amersham Biosciences Corp., Piscataway, NJ, USA) and hybridized with a 32P-labeled cDNA probe for rat MME (the same one as previously described[21]). As an internal control, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression was detected on the
**Fig. 1.** Bezafibrate (BZF) suppresses the development of antiglomerular basement membrane (GBM) glomerulonephritis. Photomicrographs were representative kidney sections on day 7. The severity of anti-GBM glomerulonephritis was markedly attenuated by the treatment with more than 133 mg/kg of BZF, whereas rabbit anti-GBM Ig was equally deposited along capillary walls of glomeruli. (A) Paraffin sections were stained with periodic acid-Schiff (PAS). Panel a, Untreated normal rats (negative control; without injection of anti-GBM or BZF treatment). Panel b, Positive control rats (with injection of anti-GBM, without BZF treatment). Panel c, Diseased rats treated with BZF at 44 mg/kg. Panel d, At 133 mg/kg. Panel e, At 400 mg/kg (original magnification ×200). (B) Rabbit anti-GBM Ig deposited along the glomerular capillary wall was detected in frozen sections by antirabbit Ig peroxidase system. Photomicrographs in panels f to j were from the same kidneys as panels a to e in (A), respectively (original magnification ×200). (C) The percentage of diseased glomeruli accompanied by necrotizing glomerulitis and/or crescentic formation in kidney sections from each group was evaluated in around 100 glomeruli (N = 6). *P < 0.001; **P < 0.01 vs. the positive control group. Error bars represent SE.

**Fig. 2.** Bezafibrate (BZF) inhibits the infiltration of ED-1+ cells in glomeruli. (A) Paraffin sections from each group were stained with antirat ED-1 antibodies. High numbers of ED-1+ infiltrates were observed in glomeruli of positive control rats (panel b). The infiltration of ED-1+ cells were unchanged in rats with lower dose of BZF (44 mg/kg) (panel c), but clearly diminished in rats with 133 or 400 mg/kg of BZF (panel d or panel e, respectively). Especially, the infiltration in rats treated by 400 mg/kg of BZF (panel e) was markedly suppressed and almost equal to that in negative control rats (panel a) (original magnification ×200). (B) Thirty glomeruli were evaluated and the number of ED-1+ cells in glomerulus were counted. The values were means of the numbers (N = 6). *P < 0.001; **P < 0.01 vs. the positive control group. Error bars represent SE. GBM is glomerular basement membrane.
were pulsed with 1 or 300 l of Falcon, Ijamsville, MD, USA) with BZF at 0, 30, 100, 44, 133, and 400 mg/kg/day (Sigma Aldrich Japan, Tokyo, Japan) at 0 or 5 l/mL. The cells were washed twice in phosphate-buffered saline (PBS) and suspended in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum (FCS). Cells were cultured suspended in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum (FCS). Cells were harvested from normal rats and prepared into single cell suspensions with a metal screen. Red blood cells were lysed by incubation in a hypotonic solution (0.83% NH₄Cl and 20 mmol/L Tris, pH 7.6). Cells were then isolated and washed twice in PBS before being used for the experiments. The cells were incubated in a 24-well plate at 1 × 10⁶ cells/well in 96-well plates (No.353072) (BD Biosciences Corp.) at 48 hours and harvested 24 hours later. The incorporated [³H]-thymidine was counted in a β-scintillation counter.

Cells were lysed by incubation in a hypotonic solution (0.83% NH₄Cl and 20 mmol/L Tris, pH 7.6). Cells were washed twice in phosphate-buffered saline (PBS) and suspended in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum (FCS). Cells were cultured at 1 × 10⁶ cells/well in 96-well plates (No.353072) (BD Falcon, Ijamsville, MD, USA) with BZF at 0, 30, 100, or 300 μmol/L and simultaneously with Con A (Sigma Aldrich Japan, Tokyo, Japan) at 0 or 5 μg/mL. The cells were pulsed with 1 μCi/well [³H]-thymidine (Amersham Biosciences Corp.) at 48 hours and harvested 24 hours later. The incorporated [³H]-thymidine was counted in a β-scintillation counter.

### Statistical analysis

The results are expressed as means ± SE. The significance of differences between parameters of the groups were tested with unpaired or paired Student t test.

### RESULTS

#### BZF suppresses the development of anti-GBM glomerulonephritis

Figure 1A shows typical histologic features of glomeruli from each group 7 days after injection of anti-GBM serum. Severe pathologic changes such as necrotizing glomerulitis, crescent formation, mesangial/endo-capillary cell proliferation, and glomerular hypertrophy were observed in rats injected with anti-GBM serum (positive control) (Fig. 1A, panel b). In rats treated with more than 133 mg/kg/day of BZF, especially with its higher dose (400 mg/kg/day), the induction of glomerulonephritis was attenuated in both severity and extent of diseased glomeruli (Fig. 1A, panels d and e), whereas rabbit Ig was equally deposited along glomerular capillaries in the groups injected with anti-GBM serum (Fig. 1B). The percentage of diseased glomeruli was evaluated in Figure 1C, resulting in a significant reduction of glomerular injury in groups treated with more than 133 mg/kg of BZF in a dose-dependent fashion. Since the importance of ED-1+ Mø and CD8+ lymphocytes in the development of this disease model was revealed in previous studies [16, 18–21], the infiltration of the cells into glomeruli was examined using immunohistochemistry (Fig. 2A). The number of ED-1+ cells per glomerulus on day 7 decreased in the groups treated with more than 133 mg/kg of BZF (Fig. 2B). A small number of CD8+ cells were observed in glomeruli of positive controls and rats treated with 44 mg/kg of BZF on day 7, but not in rats effectively treated with BZF (data not shown). Moreover, the amount of urinary protein on day 6 significantly diminished in rats treated with the higher doses of BZF (Fig. 3) in parallel with the attenuation of glomerular injuries. These data indicated that BZF effectively suppressed the development of anti-GBM glomerulonephritis in a dose-dependent manner at doses more than 133 mg/kg.

There were no dead rats in any groups during the experiment. Although fibrates are known to induce liver injury in rodents at toxic doses [24], there was no abnormality in livers by macroscopic and microscopic observations, even in rats treated with the highest dose of BZF (data not shown). The other parameters on day 7 were summarized in Table 1. A representative renal function, creatinine clearance, was slightly impaired in the diseased rats and tended to be improved in the BZF-treated groups, but there were not significant differences. Serum creatinine levels were not significantly different. Spleens cells harvested from rats treated with the highest dose of BZF were fewer than those of positive controls, whereas the number of leukocytes in peripheral blood was not significantly different among the groups. The parameters of lipid profiles, total cholesterol and triglycerides, of BZF-treated groups decreased compared with untreated diseased rats. Body weights of BZF-treated rats at 400 mg/kg diminished compared with those of positive controls. The levels of BZF in sera of rats treated with 133 or 400 mg/kg at 7 hours after the last administration on day 7 were 68.2 or 127.7 μg/mL (188 or 353 μmol/L; FW of BZF, 361.83), respectively. In the anti-GBM glomerulonephritis model, host antibodies against heterologous rabbit Ig fixed to rat

### Fig. 3. Bezafibrate (BZF) decreases the excretion of urinary protein.

The amount of protein in urine (mg/dL) on day 6 was standardized by that of creatinine in urine (mg/dL) in the groups (N = 6). *P < 0.01; **P < 0.05 vs. the positive control group. Error bars represent SE. The significance of differences between parameters of the groups was tested with unpaired or paired Student t test. The results are expressed as means ± SE. The significance of differences between parameters of the groups were tested with unpaired or paired Student t test.
GBM start to participate in glomerular injury from day 5 to 7 (autologous phase) [15]. However, the antirabbit Ig Ab titers in sera on day 7 were low and were not significantly different among the groups (data not shown).

**BZF started even after the induction of anti-GBM glomerulonephritis attenuates the disease**

Next, we attempted to examine whether treatment with BZF was also effective even after onset of the glomerulonephritis. Anti-GBM serum was injected (on day 0) and the rats were treated with either vehicle or BZF (400 mg/kg/day) from day 3 to day 7. On day 3, when BZF was started, glomerular injuries such as glomerular cell proliferation was already marked (Fig. 4A). On day 7, the glomerular injury in the BZF-treated rats was clearly mild when compared with vehicle-treated controls, whereas rabbit Ig was equally deposited along glomerular capillaries (Fig. 4B and C). The infiltration of ED-1+ cells in glomeruli was also reduced in the BZF-treated rats (Fig. 5). The amount of proteinuria from the BZF-treated rats on day 6 was significantly lower than that of vehicle-treated controls (Fig. 6).

**Reduced expression of MME in kidneys of BZF-treated rats**

We previously found MME as a tissue injury molecule in the early phase of this glomerulonephritis model [21]. To examine whether BZF reduced the expression of MME in kidneys of diseased rats, Northern blot analyses were performed. As shown in Figure 7, mRNA expression of MME, which was induced in diseased kidneys, decreased in groups effectively treated with BZF in accordance with the attenuation of glomerular injury. This finding suggested that BZF suppressed anti-GBM glomerulonephritis, at least in part, by down-regulation of MME expression in kidneys.

**BZF suppresses mitogen-induced proliferation of spleen cells**

Fibrates are known to regulate various immune reactions [3, 7, 25, 26] and are now considered as more general immunosuppressive agents [27]. Then, in order to investigate whether the attenuation of anti-GBM glomerulonephritis was exerted by immunosuppressive activity of BZF, we carried out proliferation assay using normal rat spleen cells as responders and Con A as a mitogen. The thymidine-incorporation into spleen cells stimulated by mitogen was strongly suppressed by BZF at 30 μmol/L or greater as shown in Figure 8. This finding indicated that BZF had an antiproliferative effect on immune cells at concentrations equivalent to, or less than, those in sera of rats effectively treated with BZF.

**DISCUSSION**

This study showed the suppressive effect of BZF on the development of rat anti-GBM glomerulonephritis. The disease activity of the glomerulonephritis evaluated by histologic appearance and proteinuria was attenuated not only by the pretreatment, but also by the treatment even after onset of the disease. The infiltration of ED-1+ Mø/Mo into glomeruli, and the expression of a glomerular injury molecule, MME, in kidneys were diminished in rats treated with BZF. The proliferation of spleen cells stimulated by mitogen was inhibited in vitro by BZF at concentrations equivalent to those in sera of rats effectively treated with BZF.
Bezafibrate suppresses antiglomerular basement membrane (GBM) glomerulonephritis even after induction of the disease. (A) The photomicrograph was the glomerulus on day 3 after injection of anti-GBM serum. The crescent formation and necrosis of glomerular capillaries were already obvious. The administration of BZF (400mg/kg) was started from day 3 (original magnification ×200). (B) Photomicrographs were representative kidney sections on day 7. The severity of anti-GBM nephritis was attenuated by the treatment with BZF (panel b vs. panel c). Panel a, Untreated normal rats (negative control; without injection of anti-GBM or BZF treatment). Panel b, Positive control rats (with injection of anti-GBM, without BZF treatment). Panel c, Diseased rats treated with BZF at 400 mg/kg from day 3 to 7. Photomicrographs detecting rabbit anti-GBM Ig deposition (panels d to f) were from the same kidneys as panels a to c, respectively. Rabbit anti-GBM Ig was equally deposited along capillary walls of glomeruli in diseased rats with or without BZF treatment (panels e and f) (original magnification ×200). (C) The percentage of the diseased glomeruli in kidney sections from each group was evaluated in around 100 glomeruli (N = 6). *P < 0.001 vs. the positive control group. Error bars represent SE.

Bezafibrate (BZF) started from day 3 diminishes infiltration of ED-1+ cells. (A) Paraffin sections from each group were stained with anti-rat ED-1 antibody. ED-1+ infiltrates were diminished in BZF-treated rats (panel c) when compared with positive control rats (panel b). Panel a, untreated normal rats (original magnification ×200). (B) Thirty glomeruli were evaluated and the number of ED-1+ cells in the glomerularis were counted. The values were means of the numbers (N = 6). *P < 0.001 vs. the positive control group. Error bars represent SE. GBM is glomerular basement membrane.

Bezafibrate (BZF) started from day 3 diminishes the excretion of urinary protein. The amount of protein in urine (mg/dL) on day 6 was standardized by that of creatinine in urine (mg/dL) in the groups (N = 6). *P < 0.05 vs. the positive control group. Error bars represent SE. GBM is glomerular basement membrane.

Inflammation were enhanced in PPARα-deficient mice [25, 29, 30]. In addition, fibrates did not suppress the induction of proinflammatory cytokines in PPARα-deficient mice, demonstrating that the effect was
PPARα-dependent [25]. PPARα and its ligands, fibrates, exerted anti-inflammatory actions by interfering with signal transductions of cytokines, including nuclear factor-κB (NF-κB) and activating protein (AP-1) pathways [13, 25, 29]. Recently, it was proposed that a fibrate, WY14643, might be considered as an immunosuppressive agent since it suppressed more general activities of immune cells, including mitogen-activated proliferation and antigen-specific IgG production [27]. Because effective levels of BZF in serum and culture of experiments in our current study were equivalent to those employed in the previous reports with BZF or other fibrates [25–27, 31, 32], the suppressive effect of BZF on anti-GBM glomerulonephritis might be brought about by these immunoregulatory abilities as a fibrate. In addition, it is possible that BZF inhibited signaling events elicited by proinflammatory cytokines in renal resident cells as well, such as glomerular endothelial cells, podocytes, and proximal tubular cells. Since there have recently been reports showing PPARα and/or β were expressed in these cells [2, 33, 34], BZF might suppress responses of glomerular resident cells against the action of proinflammatory cytokines released from activated immune cells; for example, production of chemokines/cytokines and expression of adhesion molecules in glomeruli, which could promote local inflammation further. Moreover, because PPARα expressed in proximal tubules plays an important role in maintaining basic cell functions, such as reabsorption of albumin [35], and fibrates protect tubular cells from ischemia [36] and cisplatin-induced acute renal failure [37], BZF might maintain tubular functions and reduce proteinuria through activating PPARα in these cells under the inflammatory condition.

Part of immunosuppressive actions by WY14643, were recently reported to be independent of PPARα pathway [27]. When compared with the findings presented in studies with WY14643 [27, 32], the present results with BZF seemed to be compatible with those, in terms of decreasing number of spleen cells in vivo and inhibiting mitogen-activated proliferation of spleen cells in vitro. However, it could not be clarified in the present study whether antiglomerulonephritis activity of BZF was dependent on the PPARα pathway because it was not carried out using PPARα-deficient animals. Recently, it has been reported that, in contrast to WY14643, the...
expression of genes induced by BZF was partly mediated by PPARβ although mainly mediated by PPARα [38]. The antiglomerulonephritis activity of BZF could be dependent on PPARβ pathway. It could be considered, in either case, that BZF suppressed the glomerulonephritis by inhibiting immune reactions against heterologous Ig fixed to GBM, including Mo/Mo activation accompanied by expression of tissue injury molecules such as MME.

BZF reduced mRNA expression of MME in kidneys, which was strongly induced in the glomerulonephritis model. It was unclear whether BZF directly down-regulated the transcription of MME gene in Mo/Mo or the reduction was caused by decreased number of infiltrating Mo/Mo. However, since MME was exclusively expressed in infiltrating Mo/Mo in this model, which was reported in our previous study [21], and the number of infiltrating Mo/Mo decreased in effectively BZF-treated rats in parallel with decline of MME mRNA expression, the MME depression might be mainly derived from the decreased number of infiltrating Mo/Mo.

This glomerulonephritis model was attempted to treat with BZF in a previously published paper [39]. In that study, BZF was administered at 50 mg/kg without any inhibitory effect on the development of glomerulonephritis. No significant efficacy was observed at such dose by our hands (44 mg/kg), either. The inhibitory effect on the glomerulonephritis appeared only at 133 mg/kg or more as shown in this study. Also in other papers using rodent disease models, anti-inflammatory effects of fibrates were shown around 150 mg/kg or more [11, 22, 40]. Moreover, in the present study, it was demonstrated that the glomerulonephritis was suppressed at 100 to 400 μmol/L of BZF in serum, which was compatible with other reports [22, 25–27, 31, 32]. In addition, there were no abnormal findings in livers of rats treated even with the highest dose of BZF (400 mg/kg) although fibrates induce liver injury at toxic doses in rodents [24].

CONCLUSION

BZF suppressed the development of rat anti-GBM glomerulonephritis, even if administered after the induction of the glomerulonephritis. The therapeutic effect might be exerted by the immunosuppressive action of fibrates, which has been already demonstrated in systems both in vivo and in vitro. The treatment options for crescentic glomerulonephritis are currently limited to use of a few drugs such as steroids and cyclophosphamide for anti-inflammatory. The findings in this study might have significant therapeutic implications for crescentic glomerulonephritis. The feasibility of the clinical application of fibrates for the treatment of human glomerulonephritis accompanying diffuse or focal crescent formation might need to be considered. However, a number of issues, for example, what is the appropriate dose for obtaining the therapeutic effects in human, must be, of course, determined.

ACKNOWLEDGMENTS

The authors thank Ms. Hiroko Sasaki and Ms. Kumiko Furui for their skilled technical assistance. The work was supported by a Health and Labor Science Research Grant for Research on Specific Diseases (No. 14146701 to Fumitake Gejyo) from the Ministry of Health, Labor and Welfare of Japan and Grants-in-Aid for Scientific Research (No. 16390242 to Ichiel Narita, No. 16590781 to Minoru Sakatsume) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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