Monoclonal antibody 1-22-3-induced glomerulonephritis in uninephrectomized rats as a model of progressive renal failure

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Abstract

Background. At present, there are few available animal models of progressive renal failure originating from mesangial proliferative glomerulonephritis (GN). In the current study, we examined the usefulness of anti-Thy-1 monoclonal antibody (mAb) 1-22-3-induced GN in uninephrectomized rats as a model of progressive renal failure by analysing the similarities to human disease.

Methods. GN was induced by intravenous injection of mAb 1-22-3 into uninephrectomized male Wistar rats. The natural course of the disease was analysed in this model for 47 weeks. The effect of treatment with the angiotensin-converting enzyme inhibitor, captopril, on renal functional outcome was also examined in this model for 23 weeks, beginning from 1 week after antibody injection.

Results. Injection of mAb 1-22-3 induced a persistent proteinuria during the entire study period. Animals showed a progressive decline in renal function and 63% died by week 47. Severe glomerular and tubulointerstitial lesions were consistently observed. Treatment with captopril significantly inhibited increases in proteinuria and blood pressure, and attenuated renal injury. Captopril also retarded the progression of renal failure, and decreased mortality. Finally, the level of proteinuria was significantly correlated with the rate of decline in renal function, and the reduction in proteinuria by captopril was accompanied by a slower progression of renal failure.

Conclusions. The mAb 1-22-3-induced GN in a uninephrectomized rat model simulates the clinical manifestations of human disease, indicating that this model may be useful for studying progressive renal failure and for investigating new therapeutic strategies against renal failure.

Keywords: angiotensin-converting enzyme inhibitor; anti-Thy-1 antibody; captopril; mesangial proliferative glomerulonephritis; predictors of renal outcome; proteinuria

Introduction

Many renal diseases in humans are progressive in nature and eventually result in end-stage renal disease. As a result, the number of patients with end-stage renal disease continues to increase worldwide. Chronic glomerulonephritis (GN), especially mesangial proliferative GN which includes immunoglobulin (Ig) A nephropathy, is one of the major causes of end-stage renal disease, and it has been reported that 15–40% of patients with IgA nephropathy will eventually have end-stage renal disease [1]. Several large scale clinical trials involving patients having diabetic and/or non-diabetic renal diseases recently demonstrated that renin–angiotensin inhibitors such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) reduced the level of proteinuria and slowed the rate of renal function decline to result in a reduced incidence of patients with end-stage renal disease [2–5]. Similar beneficial effects of renin–angiotensin system inhibitors on renal functional outcome have been reported in mesangial proliferative GN [4–6]. Nevertheless, renal diseases in many patients progress towards end-stage renal disease because the effects of these drugs are not sufficient. Therefore, there is a need for the development of new effective therapeutic strategies.

For the generation of new therapeutic strategies, it is essential to use animal models that simulate clinical...
manifestations of renal diseases in humans. To be clinically useful, we believe that such a model should simulate human renal diseases in their natural course as well as in histological features, predictors of renal functional outcome and responsiveness to drugs used clinically. There are many reported animal models of renal diseases that differ in etiology, including the 5/6 nephrectomized rat. However, there have been few reports on useful animal models of progressive renal failure originating from mesangial proliferative GN. Anti-Thy-1 monoclonal antibody (mAb) 1-22-3-induced GN in uninephrectomized rats has recently been used as a model of chronic mesangial proliferative GN [7–10]. This model is characterized by mesangial cell proliferation and matrix expansion, and is accompanied by persistent proteinuria, hypertension and a moderate decline in renal function [7–10]. In this model, treatment with ACEI or ARB inhibited increases in both proteinuria and blood pressure, and slowed the decline in renal function during the study period of 10 weeks [8]. These findings suggest that this model may be useful for studying progressive renal failure originating from mesangial proliferative GN. However, the natural course of the disease in this model has not been studied in detail. Previous studies using these rats as a model of chronic GN were conducted over relatively short periods, with the longest lasting 20 weeks after disease induction [9]. Furthermore, these reports did not describe mortality rates in this model. From these studies, it is not clear whether this model shows a progressive decline in renal function to eventually evolve into end-stage renal disease. Similarly, the relationship between renal functional deterioration and the level of proteinuria or blood pressure, both known predictors of renal functional outcome in humans [11–13], has not been analysed in this model.

In the present study, we aimed to demonstrate the usefulness of mAb 1-22-3-induced GN in uninephrectomized rats as a model of progressive renal failure by studying in detail the natural course of the disease for 47 weeks and by examining the effect of ACEI using the same model (data not shown). Captopril was purchased from Sigma Chemical Co. and was dissolved in 0.5% methylcellulose solution, and was administered orally by gastric gavage at a dosage of 30 mg/kg/day, twice a day for 23 weeks until sacrifice at week 24. We started treatment with captopril at week 1 because GN had already developed by this time. The amount of captopril used in later, GN was induced by an injection of 1 ml of saline containing 1 mg of mAb 1-22-3 into a tail vein under ether anaesthesia (designated MAB, n = 10). The preparation of mAb 1-22-3 has been described previously [14]. We also prepared sham-operated rats, which underwent a similar flank incision followed by kidney exteriorization only (designated SHAM, n = 10), and uninephrectomized rats (designated UNX, n = 9), and these were injected with saline without mAb 1-22-3. Urine samples were collected on day 2, on weeks 1, 2, 4, 6, 8, 12, 17, 20, 24, 28, 32, 36, 40, 44 and 47 after the intravenous injection (day 0, week 0) of saline with mAb 1-22-3 or saline alone. Blood samples (∼0.5 ml) were obtained from the subclavian vein under ether anaesthesia at weeks 1, 4, 8, 12, 17, 20, 24, 28, 32, 36, 40, 44 and 47. For histological assessment by light microscopy, right kidneys were removed at week 47. In addition, right kidneys were removed from SHAM (n = 25), UNX (n = 25) and MAB (n = 35) groups for histological assessment at weeks 1, 4, 8, 12 and 24 (five to nine animals from each group at each point in time).

Experiment I (analysis of natural course). Animals were anaesthetized by intraperitoneal injection with sodium pentobarbital (50 mg/kg), and the left kidney was removed through a flank incision. Following the operation, animals were subcutaneously injected with cefazolin sodium (Cefamezin, Fujisawa Pharmaceutical Co., Ltd, Osaka, Japan), an antibiotic, at a dose of 50 mg/kg. Two weeks later, GN was induced by an injection of saline containing 1 mg of mAb 1-22-3 into a tail vein under ether anaesthesia (designated MAB, n = 19). The preparation of mAb 1-22-3 has been described previously [14]. We also prepared sham-operated rats, which underwent a similar flank incision followed by kidney exteriorization only (designated SHAM, n = 10), and uninephrectomized rats (designated UNX, n = 9), and these were injected with saline without mAb 1-22-3. Urine samples were collected on day 2, on weeks 1, 2, 4, 6, 8, 12, 17, 20, 24, 28, 32, 36, 40, 44 and 47 after the intravenous injection (day 0, week 0) of saline with mAb 1-22-3 or saline alone. Blood samples (∼0.5 ml) were obtained from the subclavian vein under ether anaesthesia at weeks 1, 4, 8, 12, 17, 20, 24, 28, 32, 36, 40, 44 and 47. For histological assessment by light microscopy, right kidneys were removed at week 47. In addition, right kidneys were removed from SHAM (n = 25), UNX (n = 25) and MAB (n = 35) groups for histological assessment at weeks 1, 4, 8, 12 and 24 (five to nine animals from each group at each point in time).

Experiment II (effect of captopril on renal outcome). At 1 week after uninephrectomized rats received mAb 1-22-3 injection, we obtained blood and urine samples for measurement of serum and urine parameters. Based on levels of proteinuria, serum creatinine concentration and body weight, animals were randomly divided into two groups: a vehicle-treated MAB group (n = 20) and a captopril-treated MAB group (n = 19). During randomization, animals with serum creatinine of 0.9 mg/dl or more were selected because an expected rapid decline in renal function. Captopril was dissolved in 0.5% methylcellulose solution, and was administered orally by gastric gavage at a dosage of 30 mg/kg/day, twice a day for 23 weeks until sacrifice at week 24. We started treatment with captopril at week 1 because GN had already developed by this time. The amount of captopril used in this study was chosen as an optimal dosage found in preliminary experiments using the same model (data not shown). Captopril was purchased from Sigma Chemical Co. (St Louis, MO, USA). Additional animals with sham operations followed by saline injections were treated with 0.5% methylcellulose solution in a volume of 5 ml/kg, and served as the vehicle-treated SHAM group (n = 10). Thereafter, urine samples were collected at weeks 2, 4, 6, 8, 12, 16, 20 and 24 after disease induction. Blood samples were obtained from the subclavian vein under ether anaesthesia at weeks 4, 8, 12, 16 and 20, and from the abdominal aorta at week 24. At week 10,
systolic blood pressure was measured in pre-warmed, conscious rats by the tail-cuff method. Animals were not drug treated on the morning of blood pressure measurements. At week 24, the right kidney was removed and used for assessment by light microscopy.

**Proteinuria and renal function**

Fasting animals were individually housed in metabolic cages with free access to water for the collection of 24 h urine samples. Urinary protein concentration was measured by the Bradford method (BioRad, Hercules, CA, USA), using bovine serum albumin as a standard. It has been reported that the product of duration and level of proteinuria may be a useful predictor of glomerular and tubulointerstitial histological changes and the fate of renal function in IgA nephropathy [11]. Therefore, we calculated the level of cumulative protein excretion from week 0 to each point in time using following formulae:

\[
CPE1 = \frac{([UPB] + (UP1)] \times (D1))/2}{1000} \\
CPE2 = CPE1 + \frac{([UP1] + (UP2)] \times (D2))/2}{1000} \\
CPE4 = CPE2 + \frac{([UP2] + (UP4)] \times (D4))/2}{1000} \\
CPE24 = CPE20 + \frac{([UP20] + (UP24)] \times (D24))/2}{1000}
\]

where \(CPE1\) = level of cumulative protein excretion from week 0 to \(n\) (g), \(UPB\) = an average level of proteinuria in the vehicle-treated SHAM group at week 1 as a basal value (mg/day), \(UPn\) = level of proteinuria at week \(n\) (mg/day), \(D1\) = number of days between week 0 and 1, \(D2\) = number of days between week 1 and 2, \(D4\) = number of days between week 2 and 4 and \(D24\) = number of days between week 20 and 24.

Serum creatinine, blood urea nitrogen (BUN) and urinary creatinine concentrations were measured using an autoanalyzer (TBA-80FR, Toshiba, Tokyo, Japan). The doubling of serum creatinine concentration, which is used clinically as an index of renal function deterioration, was evaluated and defined as twice the basal level of creatinine concentration (week 1), and the percentage of animals having doubled creatinine at each point in time was calculated. For comparison, we selected week 1 as a time point for the basal level in Experiment I as well as in Experiment II. We found that several animals died before they had reached the doubling of creatinine: this was probably due to end-stage renal disease, because serum creatinine concentration in these animals had already increased. Therefore, we designated these animals as having reached the doubling of creatinine. It has been reported that in most patients with chronic renal failure, the reciprocal of serum creatinine concentration (1/Cr) declines linearly with time as chronic renal failure progresses [15]. Therefore, we analysed the relationship between 1/Cr and time, and defined the slope of the regression line (1/Cr slope) as the rate of decline in renal function. In this model, the renal function declined transiently at week 1, then tended to recover, and declined again from week 4. We therefore used the values at week 4 as the first point in time for this analysis.

**Light microscopy**

Tissue samples for light microscopic assessment were fixed with 4% paraformaldehyde or 10% neutral-buffered formalin, embedded in paraffin, cut into 3μm sections and stained with periodic acid-Schiff (PAS) reagent. The affected area of the glomerular lesion (mesangial matrix expansion) was evaluated and was semi-quantitatively scored. Approximately 50 full-sized, randomly selected glomeruli were examined from each specimen, and the lesion was graded from 0 to 4+, according to the percentage of glomerular involvement as follows: grade 0, 0–4%; grade 1+, 5–24%; grade 2+, 25–49%; grade 3+, 50–74%; grade 4+, 75% or more. In addition, the affected area of the tubulointerstitial lesion, including tubular dilatation, atrophy and basophilia, and interstitial inflammation and fibrosis, in the cortical area was evaluated, semi-quantitatively scored, and graded from 0 to 4+, according to the percentage of affected area as follows: grade 0, no lesion; grade 1+, 1–4% of the observed area; grade 2+, 5–24% of the observed area; grade 3+, 25–49% of the observed area; grade 4+, 50% or more of the observed area. The sections were examined in a blinded manner.

**Statistical analysis**

Data were expressed as means±SEM. Statistical significance was analysed using Student’s t-tests, Aspin–Welch’s t-tests, or Mann–Whitney U-tests. Comparisons between groups on the doubling of creatinine or mortality were performed using a log-rank test. The Pearson r correlation coefficient was calculated using individual animal data. A P-value of <0.05 was considered significant.

**Results**

**Experiment I**

**Proteinuria.** The time course of proteinuria is shown in Figure 1A. The level of proteinuria in the MAB group peaked on day 2 after disease induction, then decreased until week 4, and finally increased progressively until week 40. In the UNX group, proteinuria began to increase at week 17 after saline injection, although the amount was less than that in the MAB group. In the SHAM group, proteinuria began to increase at week 32 after saline injection, but the amount was less than that in the UNX group. Similar results were obtained when the data were adjusted for body weight (data not shown).

**Renal function.** In the MAB group, renal function assessed by BUN level, serum creatinine concentration and creatinine clearance, declined transiently at week 1, recovered at week 4, then declined again (Figure 1B–D). These animals showed a progressive decline in renal function. Animals that doubled serum creatinine concentration first appeared at week 12, and by week 47, up to 89% showed doubled creatinine (Figure 2A). Similarly, animals died beginning at week 14, and the mortality rate reached 63% by week 47 (Figure 2B). In addition, 1/Cr in individual animals declined linearly with time (data not shown). In the UNX group, renal function was reduced compared with the SHAM group during the study period.
(Figure 1B–D), and 22% of UNX animals reached a doubling of serum creatinine concentration by week 47 (Figure 2A), although no animals died by week 47 (Figure 2B). In the SHAM group, renal function was mostly stable throughout the study period (Figures 1B–D and 2).

**Histological findings.** In the MAB group, mesangial cell proliferation and matrix expansion were evident at week 1, after which there were increases in sclerotic lesions, including adhesion to the Bowman’s capsule (Figure 3). This group also showed tubulointerstitial changes, including tubular basophilia, dilatation, and slight interstitial changes such as cellular infiltration and fibrosis at weeks 1–8. After week 8, interstitial cellular infiltration and fibrosis as well as tubular atrophy were evident. The severity of the glomerular and tubulointerstitial lesions were less during early stage (until week 12) than in later stages (weeks 24 and 47). In the UNX group, glomerular injury was minimal until week 12, after which mesangial matrix expansion appeared (Figure 4). Tubulointerstitial lesions were not observed until week 4, after which the similar lesion to those in the MAB group appeared. In the SHAM group, glomerular injury was minimal until week 24, and mesangial matrix expansion appeared at week 47. In this group, tubulointerstitial lesions were not observed until week 24, and appeared at week 47. The score for glomerular and tubulointerstitial injuries in the MAB group increased at week 1, and did not change throughout the study period; however, the severity of the lesions were different between early and later stages, as previously described (Figure 4).

**Experiment II**

**Body weight gain and proteinuria.** Body weight was lower in the vehicle-treated MAB group than in the vehicle-treated SHAM group throughout the study period (Figure 5A). There was no difference in body weight gain between the vehicle- and captopril-treated MAB groups. The level of proteinuria was significantly lower in the captopril-treated MAB group than in the vehicle-treated MAB group at weeks 8 and 12. It gradually increased thereafter, but remained lower than in the vehicle-treated MAB group until the end of the experiment (Figure 5B). Similarly, the level
of cumulative protein excretion was lower in the captopril-treated MAB group than in the vehicle-treated MAB group throughout the study period (Figure 5C).

Renal function. The percentage of animals reaching a doubling of serum creatinine was significantly lower in captopril-treated MAB rats than in vehicle-treated MAB rats ($P<0.05$), and was lowered by 71% at week 24 (Table 1). Similarly, the mortality rate was lower in the captopril-treated MAB group than in the vehicle-treated MAB group, and was decreased by 60% at week 24, although this difference did not reach statistical significance. Moreover, 1/Cr in individual animals with chronic renal failure declined linearly with time (Figure 6A). The rate of renal function decline,
as assessed by 1/Cr slope, was significantly slower in the captopril-treated MAB group than in the vehicle-treated MAB group (P < 0.05, Figure 6B).

**Blood pressure and histological findings.** Systolic blood pressure at week 10 was significantly higher in the vehicle-treated MAB group than in the vehicle-treated SHAM group (P < 0.001), and captopril significantly inhibited the elevation in systolic blood pressure [vehicle-treated SHAM group, 133 ± 2; vehicle-treated MAB group, 173 ± 6; captopril-treated MAB group, 150 ± 5 mmHg (P < 0.01)]. Histology showed that the glomerular and tubulointerstitial injuries were attenuated in the captopril-treated MAB group, and scores for injury were significantly lower than in the vehicle-treated MAB group at week 24 (glomerular injury: vehicle-treated SHAM group, 0.10 ± 0.10; vehicle-treated MAB group, 1.09 ± 0.15 (P < 0.05); tubulointerstitial injury: vehicle-treated SHAM group, 0.10 ± 0.10; vehicle-treated MAB group, 3.33 ± 0.22; captopril-treated MAB group, 2.38 ± 0.26 (P < 0.05)).

Analyses of the predictors of renal functional outcome. It has been reported that blood pressure and the level of proteinuria are predictors of renal functional outcome in patients with chronic renal diseases, including IgA nephropathy [11–13]. Therefore, we analysed the relationship between these parameters and renal outcome in this model. Systolic blood pressure at week 10 significantly correlated with 1/Cr slope (Figure 7A). The level of cumulative protein excretion from disease induction to weeks 8 or 24 also significantly correlated with 1/Cr slope (Figure 7B and C). Similarly, the level of proteinuria at week 8 significantly correlated with 1/Cr slope (data not shown). Furthermore, the level of cumulative protein excretion up to week 24 significantly correlated with the severity of glomerular and tubulointerstitial injury at week 24 (Figure 7D and E). The inhibition of systolic blood pressure increases and the level of proteinuria by captopril were accompanied by a decrease in 1/Cr slope. Moreover, the inhibition of an increase in the level of cumulative protein excretion by captopril was accompanied by less glomerular and tubulointerstitial injury.

**Discussion**

Many patients with mesangial proliferative GN, including IgA nephropathy, show a progressive decline in renal function and persistent proteinuria [1]. In the present study, uninephrectomized rats injected with mAb 1-22-3 (MAB group) showed persistent proteinuria during the study period (Figure 1A). Similar results were obtained when the data were adjusted for body weight, indicating that the persistent proteinuria was not caused by an increase in body weight. Renal function declined transiently at week 1, recovered at week 4, then declined again (Figure 1B-D). We speculate that this biphasic change in renal function was caused by a single mechanism; that is, the first decline was caused by acute glomerular injury, and the second was due to a progression of tubulointerstitial injury, as described by Matsumoto et al. [16]. Renal function declined progressively. In fact, 89% of animals reached a doubling of serum creatinine concentration and 63% of animals died, probably due to end-stage renal disease by week 47 (Figure 2). We also found that 1/Cr in individual animals with chronic renal failure declined linearly with time (Figure 6A), as has been

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**Fig. 4.** Changes in scores for glomerular (A) and tubulointerstitial injuries (B) in the MAB, UNX and SHAM groups. The scores for glomerular and tubulointerstitial injuries in the MAB group increased at week 1, and did not change for the remainder of the study. However, the score for glomerular injury in the UNX group began to increase at week 24, and the score for tubulointerstitial injury increased at week 8. In the SHAM group, both scores increased at week 47. Data are expressed as means±SEM. **: P < 0.05 compared with the SHAM group. *: **: P < 0.01 compared with UNX group. The glomerular scores at weeks 4, 8 and 12 in the SHAM group, the tubulointerstitial scores at weeks 1, 4, 8, 12 and 24 in the SHAM group, and at weeks 1, 4 and 12 in the UNX group were all zero, and the tubulointerstitial scores at week 24 in the UNX group were all one; therefore, the values at these points could not be used for statistical analysis. The number of animals in the SHAM and UNX groups was five at each point. The number of animals in the MAB group was 8, 9, 7, 6, 5 and 7 at weeks 1, 4, 8, 12, 24 and 47, respectively.
shown in human disease [15]. Previous studies using this as a model of chronic GN were conducted over relatively short time periods, with a maximum of 20 weeks after disease induction [9]. These studies indicated that this model shows persistent proteinuria accompanied by a moderate decline in renal function. However, the time course of renal function in this model has not been studied in detail, and these studies did not report mortality rates in this model. Therefore, it was not clear whether this model showed a progressive decline in renal function to eventually result in end-stage renal disease. The present findings clearly indicate that renal disease in this model is progressive in nature, and many animals eventually developed end-stage renal disease. Therefore, these results suggest that this model simulates the natural course of human progressive renal failure originating from mesangial proliferative GN.

We observed several pathological changes in this model, such as the mesangial cell proliferation, matrix expansion and tubulointerstitial injury (Figures 3 and 4). These changes have also been observed in patients with progressive IgA nephropathy [1]. Of these alterations, mesangial cell proliferation is the most characteristic of IgA nephropathy. It has been reported that platelet-derived growth factor (PDGF) can induce the proliferation of mesangial cells, and that an increased expression of PDGF is observed in glomeruli of patients with IgA nephropathy [17]. Therefore, it is possible that PDGF contributes to the development of mesangial proliferative GN in humans. In uninephrectomized rats injected with mAb 1-22-3, blockade of PDGF resulted in a reduction of the mesangial proliferative changes and prevented renal scarring [10]. These results suggest that this model simulates histological features of the human disease, including the pathogenesis of mesangial proliferative GN.

It is well known that most patients with chronic renal diseases are complicated by hypertension. Renin–angiotensin system inhibitors are considered to be the most effective antihypertensive drugs for renoprotection, even though achieved blood pressures are comparable [2]. In patients with mesangial proliferative GN, renin–angiotensin system inhibitors may exert beneficial effects on renal functional outcome [4–6]. However, the effect of renin–angiotensin system inhibitors on proteinuria in these patients is not sufficient, and renal disease in many subjects progresses

Table 1. Effect of captopril on renal functional outcome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vehicle-treated SHAM</th>
<th>Vehicle-treated MAB</th>
<th>Captopril-treated MAB</th>
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<tbody>
<tr>
<td>Doubling of Cr (%)</td>
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<td>8 0 5 0</td>
<td>16 0 55 16*</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>1 0 0 0</td>
<td>8 0 0 0</td>
<td>16 0 25 11</td>
</tr>
</tbody>
</table>
| Doubling of Cr: cumulative incidence of animals reaching the doubling of serum creatinine concentration. *Doubling of Cr in the captopril-treated MAB group was significantly lower than in the vehicle-treated MAB group (P<0.05). Mortality in the captopril-treated MAB group tended to be lower than that in vehicle-treated MAB group, although it did not reach a statistically significant difference.
towards end-stage renal disease. In a previous study using uninephrectomized rats injected with mAb 1-22-3, treatment with ACEI or ARB inhibited increases in both proteinuria and in blood pressure, and slowed the decline in renal function during the study period of 10 weeks [8]. In addition, these drugs were more renoprotective than hydralazine, an anti-hypertensive drug, even though blood pressure was controlled at a comparable level in both groups [8]. However, it was not clear whether the renin–angiotensin system inhibitor slowed the rate of renal function decline in this model when the study period was expanded. In the present study, treatment with captopril for 23 weeks in the MAB group inhibited increases in proteinuria and blood pressure, slowed the rate of decline in renal function and reduced mortality (Figures 5B, C and 6B, and Table 1). Captopril also attenuated the severity of glomerular and tubulointerstitial injury. On the other hand, there was no difference in body weight gain between the vehicle-treated MAB and captopril-treated MAB groups (Figure 5A), suggesting that the amount of dietary protein ingestion in both groups was similar. These results indicate that captopril may improve renal outcome in this model. The present study also showed that renal disease in this model tended to progress towards end-stage renal disease, despite the effectiveness of captopril on blood pressure and proteinuria (Figures 5B, C and 6B, and Table 1). This effect may be explained by an insufficient inhibitory effect of captopril on increases in proteinuria (Figure 5B and C). Collectively, these results suggest that this model simulates human disease and its responsiveness to anti-hypertensives.

Blood pressure has been reported to be a predictor of renal functional outcome in chronic renal diseases, including IgA nephropathy [12,13]. In the present study, we found that systolic blood pressure at week 10 correlated with the rate of decline in renal function in the MAB groups (Figure 7A). In addition, the inhibition of blood pressure elevation by captopril was accompanied by a slower progression of renal failure. These results indicate that systolic blood pressure is one of the predictors of renal function outcome in this model.

The level of proteinuria has been recognized as an additional predictor of renal functional outcome in chronic renal diseases [3,11–13]. It has also been reported that the product of duration and level of proteinuria may be a useful predictor of glomerular and tubulointerstitial histological changes and of the fate of renal function in IgA nephropathy [11]. Proteinuria is not only a marker of glomerular injury but is also a cause of tubulointerstitial injury [18]. Therefore, reductions in proteinuria are expected to produce a slowing of clinical renal function decline [3]. In the present study, we demonstrated that the level of cumulative protein excretion from disease induction to weeks 8 or 24 correlated with the rate of decline in renal function in the MAB groups (Figure 7B and C). In addition, inhibition of proteinuria increases by captopril was accompanied by a slower progression of renal failure. Furthermore, we showed that the level of cumulative protein excretion from disease induction to week 24 correlated with the severity of glomerular and tubulointerstitial injury (Figure 7D and E). These results indicate that the level of proteinuria is one predictor of renal functional outcome in this model. From these findings, we believe that this model simulates human disease in terms of renal functional outcome predictors.

In summary, the present findings suggest that mAb 1-22-3-induced GN in uninephrectomized rats simulates the clinical manifestations of progressive renal failure originating from mesangial proliferative GN, including the natural course, histological features, predictors of renal functional outcome and responsiveness to clinically used drugs. From these findings, we conclude that mAb 1-22-3-induced GN in uninephrectomized rats provides a useful model of progressive renal failure originating from mesangial proliferative GN. Thus, this model will be valuable for investigating new therapeutic strategies in progressive renal failure.


11. Eiro M, Katoh T, Kuriki M, Asano K, Watanabe K, Watanabe T. The product of duration and amount of proteinuria (proteinuria index) is a possible marker for glomerular and tubulointerstitial damage in IgA nephropathy. *Nephron* 2002; 90: 432–441


Received for publication: 28.1.05
Accepted in revised form: 15.7.05