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BRIEF REPORT

Poor renal outcomes in patients with anti-neutrophil cytoplasmic antibody-associated crescentic glomerulonephritis and normal renal function at diagnosis

Hironari Hanaoka[1] · **Yuichiro Ota**[1] · **Tsutomu Takeuchi**[1] · **Masataka Kuwana**[1,2]

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Abstract The aim of this study is to investigate the renal outcomes of anti-neutrophil cytoplasmic antibody (ANCA)-associated crescentic glomerulonephritis in patients with normal estimated glomerular filtration rate (eGFR) at diagnosis. Twenty-seven patients with biopsy-proven ANCA-associated crescentic glomerulonephritis were retrospectively recruited and were divided into 12 with normal eGFR (≥60 ml/min/1.73 m^2) and 15 with low eGFR (<60 ml/min/1.73 m^2) at baseline. Clinical and renal pathological findings at diagnosis and renal outcomes for up to 3 years were compared between the two groups. Two patients in the low eGFR group died of severe bacterial pneumonia. In the normal eGFR group, the following characteristics were observed: younger age at diagnosis ($p = 0.04$), diagnosis of granulomatosis polyangiitis (GPA) ($p < 0.01$), and lower frequency of cyclophosphamide treatment ($p = 0.03$). On renal pathological analysis, the normal eGFR group had a significantly lower proportion of cellular crescent formation ($p = 0.01$), fibrinoid necrosis ($p = 0.01$), interstitial fibrosis ($p = 0.02$), and tubular atrophy ($p = 0.02$). As a result, the two groups did not significantly differ in remission rates, relapse rates, Birmingham vasculitis score, vasculitis damage index, or eGFR on 3-year follow-up. Patients with biopsy-proven ANCA-associated glomerulonephritis and normal eGFR at diagnosis have poor renal outcomes and may require standard intensive immunosuppressive treatment to prevent accrual of damage.

Keywords ANCA-associated glomerulonephritis · Normal estimated glomerular filtration rate · Prognosis · Vasculitis

Introduction

The prognosis of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitis is still devastating [1]. In particular, generalized ANCA-associated glomerulonephritis is associated with a poor prognosis for both patient and renal survival [2]. The benefit of early diagnosis and early therapeutic intervention has been established for many rheumatic diseases, including rheumatoid arthritis, and an improved prognosis has been reported for patients who receive this early intervention compared to those who do not [3, 4]. Since the concept of ANCA-associated vasculitis has been widely accepted, early diagnosis is occasionally made in clinical settings. Such patients with biopsy-proven ANCA-associated glomerulonephritis often have normal estimated glomerular filtration rate (eGFR) at diagnosis. However, the clinicopathological features and prognosis of these patients have not been investigated in detail. Recently, histopathological classification of ANCA-associated glomerulonephritis has been developed to distinguish severity among patients [5]. This scheme is a practical and informative means of predicting the prognosis of patients with glomerulonephritis. However, it is difficult to be used for patients without renal insufficiency, as is based on data from two randomized controlled trials that investigated patients with severe renal insufficiency [6, 7].

Here, to better understand the clinical and pathological features and prognosis of patients with ANCA-associated crescentic glomerulonephritis, we comprehensively analyzed the

✉ Hironari Hanaoka
hhanaoka1208@yahoo.co.jp

[1] Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

[2] Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan

outcomes of patients with normal eGFR at diagnosis and compared them to patients with low eGFR at diagnosis.

Materials and methods

Patients

Fifty-eight consecutive Japanese patients who were diagnosed with ANCA-associated vasculitis according to the classification of the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [8] and had visited Keio University Hospital from 1999 to 2010 were assessed for eligibility. Enrollment criteria included (i) newly diagnosed, (ii) renal biopsy-proven ANCA-associated glomerulonephritis, and (iii) observation period >3 years unless death during follow-up. Following exclusion of inappropriate candidates, a total of 27 patients were enrolled in this study.

Patients were divided into two groups based on eGFR at baseline: a normal and a low eGFR group. Low eGFR was defined as that a rate below 59 ml/min/1.73 m^2, in accordance with chronic kidney disease (CKD) guidelines [9]. This study was approved by the Ethics Committee of Keio University. This study was a retrospective cohort using no samples other than those obtained for clinical use. In lieu of obtaining consent, public announcements of this study were posted.

Data collection

Clinical characteristics, treatment, and clinical course following initial induction therapy were retrospectively collected based on chart review.

Relevant information was obtained from all patients at baseline and 6, 12, 24, and 36 months after initial induction therapy. Data included demographic characteristics, treatment regimens, and Birmingham Vasculitis Score (BVAS) [10]. Remission was defined as an absence of clinical disease activity, as indicated BVAS of 0, and relapse was defined as an increase in the BVAS of 1 point or more. Vasculitis Damage Index (VDI) [11] was also sequentially scored at each observational period. Serum ANCA was measured with an ELISA kit (Medical and Biological Laboratories, Nagoya, Japan) according to the manufacturer's instructions. Ear, nose, and throat involvement were detected by either computed tomographic analysis or as diagnosed by an otolaryngologist. Lung involvement was revealed by X-ray or computed tomography analysis. Definitions of vasculitis-associated complications were as previously described [12].

Renal pathology

Patients underwent a renal biopsy before initial induction therapy. Specimens for light microscopy were embedded in paraffin, sectioned, and stained with Masson's trichrome, hematoxylin-eosin, periodic acid-silver methenamine (PAM), and periodic acid-Schiff (PAS) reagent. Frozen tissues were cut into 5-μm sections and incubated with fluoresceinated antisera to human IgG, IgA, IgM, C3, C4, C1q, and fibrinogen. Patients underwent light microscopy and immunofluorescence analysis and were diagnosed according to the histopathological classification of ANCA-associated glomerulonephritis [5]. Tubulointerstitial and vascular lesions were scored dichotomously according to a previously standardized protocol [13]. Interstitial fibrosis and tubular atrophy were scored semi-quantitatively.

Statistical analysis

Continuous values are shown as mean ± standard deviation (SD). Clinical characteristics between the two groups were compared using the non-parametric Mann-Whitney *U* test. Frequencies of clinicopathological characteristics were compared using the chi-square test. Relapse-free survival rates were calculated using the Kaplan-Meier method, and differences between the two groups were tested with a log-rank test.

Results

Baseline characteristics and treatment regimens

The 27 patients were divided into two groups based on eGFR level at diagnosis, with 12 in the normal eGFR group and 15 in the low eGFR group. All patients received glucocorticoid (GC) therapy at an initial dose of 1.0 mg equivalent prednisolone (PSL)/kg/day for 2 to 4 weeks. After initial therapy, PSL was tapered by 10 % of the last dose or 10 mg, as determined by rheumatologists based on their expertise. For induction therapy, all except three patients received one of the following immunosuppressive agents: intravenous cyclophosphamide (IVCY), mycophenolate mofetil (MMF), or azathioprine (AZA). The three remaining patients received PSL monotherapy. The dose of IVCY ranged from 300 to 750 mg/4-week interval for two to six courses. The initial dose of MMF was 0.5 to 1 g/day and gradually increased to 2 g/day. The dose of AZA was 50 to 100 mg/day. Following infusions of IVCY, the immunosuppressant was switched to AZA (100 mg/day) as maintenance therapy. Patients receiving MMF kept the same treatment for remission maintenance.

Clinical and renal pathological characteristics

Demographic and clinical features at baseline were compared between patients with normal and low eGFR (Table 1). Patients with normal eGFR frequently had a younger age ($p = 0.04$), diagnosis of granulomatosis polyangiitis (GPA)

Table 1 Baseline clinical and renal pathological characteristics of crescentic glomerulonephritis with or without renal dysfunction at diagnosis

Baseline characteristics	eGFR status at baseline		*p* value
	Low ($n=15$)	Normal ($n=12$)	
Sex (% female)	9 (60.0)	4 (33.3)	0.2
Age (years)	72.0 ± 15.1	60.4 ± 20.8	0.04
Diabetes mellitus (%)	1 (6.7)	1 (8.3)	0.8
Systolic blood pressure (mmHg)	139.2 ± 5.5	134.2 ± 12.1	0.4
Diastolic blood pressure (mmHg)	88.2 ± 10.1	82.1 ± 12.1	0.2
Prior use of ACEi or ARB (%)	8 (53.3)	5 (41.6)	0.5
Diagnosis			
GPA (%)	2 (13.3)	8 (66.6)	<0.01
MPA (%)	13 (86.7)	4 (33.3)	<0.01
Creatinine (mg/dl)	1.7 ± 0.7	0.7 ± 0.2	<0.01
eGFR (ml/min/1.73 m^2)	34.3 ± 13.8	84.2 ± 24.6	<0.01
CRP (mg/dl)	3.1 ± 3.7	6.7 ± 6.5	0.04
Proteinuria (g/gCr)	1.0 ± 1.1	0.4 ± 0.4	0.07
Hematuria (%)	15 (100)	12 (100)	1
Red cell cast (%)	6 (40.0)	1 (8.3)	0.06
MPO-ANCA positive (%)	13 (86.7)	8 (66.7)	0.2
PR3-ANCA positive (%)	1 (6.7)	4 (33.3)	0.4
MPO-ANCA (U/ml)	257.7 ± 237.7 ($n=13$)	72.9 ± 82.8 ($n=8$)	0.02
PR3-ANCA (U/ml)	109 ($n=1$)	175.6 ± 172.0 ($n=4$)	N/A
Ear, nose, throat involvement (%)	1 (6.7)	8 (66.7)	<0.01
Lung involvement (%)	10 (66.7)	8 (66.7)	0.7
BVAS	13.0 ± 5.2	11.2 ± 4.6	0.2
Initial prednisolone dosage (mg/day)	48.7 ± 15.1	47.7 ± 12.0	0.5
Induction therapy			
IVCY (%)	14 (93.3)	7 (58.3)	0.03
Cumulative dose (mg)	3833.3 ± 790.6	2428.6 ± 1312.4	<0.01
MMF (%)	0 (0)	1 (8.3)	0.3
PSL monotherapy (%)	0 (0)	3 (23.1)	0.03
Others (%)	1 (6.7)	1 (8.3)	0.9
Renal pathological findings			
Normal glomeruli (%)	50.5 ± 23.3	80.4 ± 9.6	<0.01
Fibrinoid necrosis (%)	14.6 ± 13.6	2.4 ± 5.6	0.01
Crescents (%)	24.3 ± 12.8	12.1 ± 9.2	0.01
Cellular	87.5 ± 23.7	66.7 ± 50.0	0.1
Fibrous	24.2 ± 16.3	13.3 ± 15.1	0.05
Global sclerosis (%)	24.6 ± 20.2	7.5 ± 8.8	0.01
Renal histological category			
Sclerotic	3 (20.0)	0 (0)	0.1
Focal	9 (60.0)	12 (100)	0.01
Crescentic	0 (0)	0 (0)	1
Mixed	3 (20.0)	0 (0)	0.1
Tubulointerstitial and vascular			
Interstitial edema (0/1)	0.5 ± 0.5	0.5 ± 0.5	0.3
Interstitial infiltrates (0/1/2/3)	1.1 ± 0.9	0.7 ± 0.7	0.09
Interstitial fibrosis (0/1/2)	1.0 ± 0.5	0.6 ± 0.5	0.02
Tubular casts (0/1)	0.5 ± 0.3	0.5 ± 0.3	0.2
Tubular necrosis (0/1)	0.3 ± 0.2	0.3 ± 0.2	0.2
Tubular atrophy (0/1/2)	1.0 ± 0.5	0.6 ± 0.5	0.02
Intraepithelial infiltrate (0/1)	0.6 ± 0.2	0.5 ± 0.3	0.3
Arteriosclerosis (0/1)	0.6 ± 0.5	0.2 ± 0.4	0.05

eGFR estimated glomerular filtration rate, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *BVAS* Birmingham Vasculitis Score, *IVCY* intravenous cyclophosphamide, *MMF*, mycophenolate mofetil; *N/A*, not applicable

($p<0.01$), and upper respiratory involvement ($p<0.01$). Although BVAS scores did not differ markedly between the two groups ($p=0.2$), higher serum C-reactive protein (CRP) levels were observed in the normal eGFR group than in the low eGFR group ($p=0.04$). Careful examination revealed no obvious cause of inflammation beyond ANCA-associated small-vessel vasculitis at baseline. Regarding initial treatment, although prednisolone dose did not differ markedly between the two groups ($p=0.5$), patients with normal eGFR showed a lower frequency ($p=0.03$) and cumulative dose ($p<0.01$) of cyclophosphamide treatment and a higher proportion of PSL monotherapy ($p=0.03$) than those in the low eGFR group.

On renal pathological analysis, proportions of cellular crescent formation ($p=0.01$), fibrinoid necrosis ($p=0.01$), interstitial fibrosis ($p=0.02$), and tubular atrophy ($p=0.02$) were significantly lower among patients in the normal eGFR group than in the low eGFR group. Further, glomeruli were more frequently normal in patients with normal eGFR than in those with low eGFR ($p<0.01$). In the normal eGFR group, all patients were classified as having the focal type ($p=0.01$). In the low eGFR group, 3 (20 %) patients were classified as having the sclerotic type; 9 (60 %), the focal type; and 3, (20 %) the mixed type on histopathological classification.

Renal outcomes and damage accrual

All patients were followed for 3 years after the start of therapy, with the exception of the two who died in the low eGFR group. The cause of death for both of these patients was severe bacterial pneumonia and unrelated to ANCA-associated small-vessel vasculitis. We had no patients who developed end-stage renal disease in this study. At 3-year follow-up, no significant differences were observed in BVAS and

cumulative remission rates between patients with normal eGFR and low eGFR (83.3 vs. 66.7 %, $p=0.27$) (Fig. 1). Although a significant difference was not seen in probability of relapse-free survival between the two groups, patients with low eGFR less frequently experienced a relapse than those with normal eGFR ($p=0.06$). Further, while eGFR level was significantly higher in patients in the normal eGFR group at 6 ($p<0.01$) and 12 ($p=0.02$) months, this difference lost significance at 3 years ($p=0.26$) (Fig. 2). VDI between the two groups was not significantly different for 3-year observation. To determine whether initial treatment influenced these results, we divided all patients with normal eGFR into two groups according to IVCY exposure. At 3-year follow-up, patients without IVCY treatment had significantly lower eGFR than those with IVCY treatment (42.1 ± 13.2 vs. 62.1 ± 10.1 ml/min/1.73 m^2, $p=0.01$).

Discussion

Our findings demonstrate that renal outcomes after 3 years were similar between patients with ANCA-associated glomerulonephritis who had normal eGFR at diagnosis and those who had low eGFR at diagnosis.

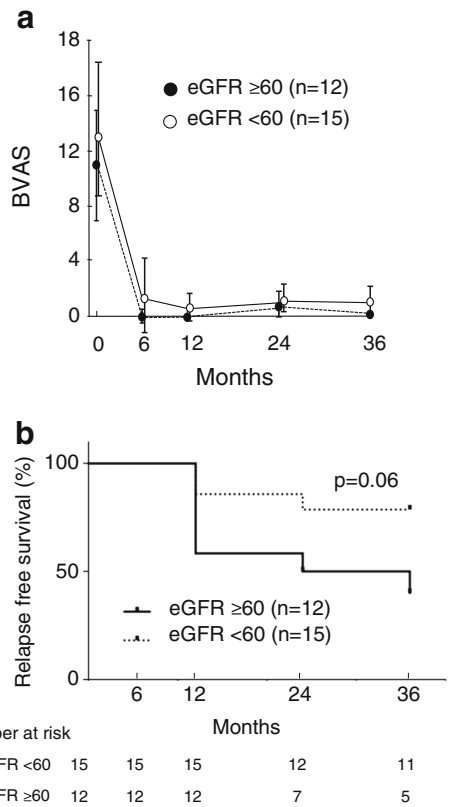

Fig. 1 Sequential BVAS (**a**) and relapse-free survival rates (**b**) for patients with normal eGFR and low eGFR (mean; 95 % confidence interval). No significant difference was observed in BVAS and relapse-free survival in the two groups. *BVAS* Birmingham Vasculitis Score, *eGFR* estimated glomerular filtration rate

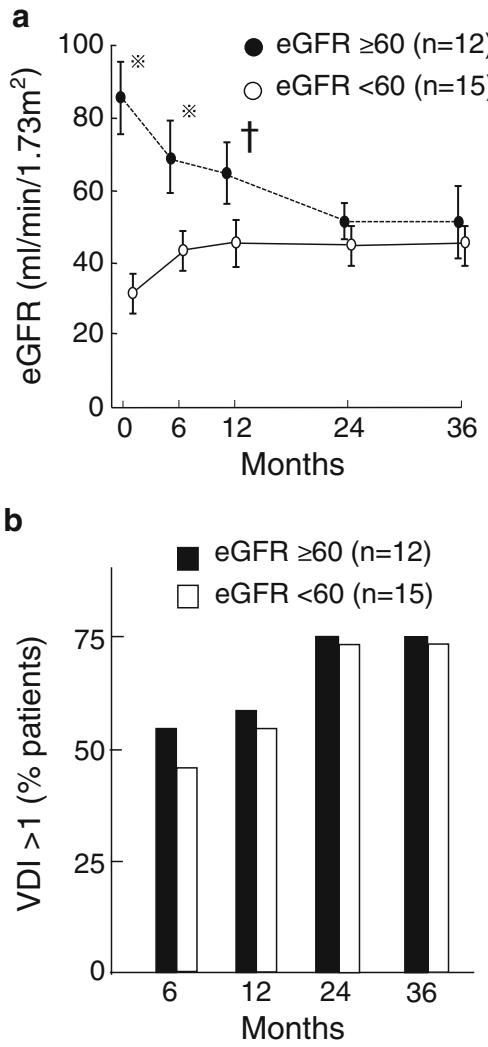

Fig. 2 Sequential eGFR (**a**) and VDI (**b**) for patients with normal eGFR and low eGFR (mean; 95 % confidence interval). While eGFR level was significantly higher in patients in the normal eGFR group at 6 and 12 months, this difference lost significance at 3 years. *VDI* Vasculitis Damage Index; *$p<0.01$ vs. eGFR <60, †$p=0.02$ vs. eGFR <60

Even with the improved prognosis following the introduction of corticosteroids and cyclophosphamide, patients with ANCA-associated glomerulonephritis still have poor outcomes overall [14]. The European Vasculitis Study Group (EUVAS) recommends that patients with serum creatinine levels below 5.7 mg/dl should be treated with prednisone and cyclophosphamide for 3 to 6 months [15]. To our knowledge, however, data concerning the management of biopsy-proven generalized ANCA-associated glomerulonephritis in patients with normal serum creatinine is limited. A number of recent randomized studies have verified the efficacy of therapeutic agents for generalized ANCA-associated glomerulonephritis, but none have conducted a sub-analysis focusing on patients without renal insufficiency [6, 7, 15, 16]. Our

present findings suggest that patients with normal renal function at diagnosis may still require standard intensive treatment to prevent damage accrual.

A recent pathological analysis of a number of predictors of renal function [17] found "percentage of normal glomeruli at first biopsy" to be an effective predictor [18]. To achieve a good renal outcome, the emergence of active vasculitis lesions has to be inhibited by immunosuppressive therapy and normal glomeruli should be protected from crescentic formation. Therefore, even when a diagnosis is made at a clinically stable or early phase, recommended initial induction therapy is still required to prevent future destruction of normal glomeruli.

McAdoo et al. recently evaluated 28 patients with renal biopsy-proven ANCA-associated necrotizing or crescentic glomerulonephritis and normal serum creatinine (<120 mmol/l) [19]. As the eGFR of these patients ranged from 50 to 132 ml/min at baseline, their renal function might have been worse than those in our study. They reported that 68 % of patients were treated with PSL and cyclophosphamide, which is closely similar to our result of 66.9 %, and concluded that the majority of patients treated with immunosuppressive treatment might have a good renal prognosis, which is consistent with our findings and hypothesis.

In our study, although a significant difference was not seen in relapse-free survival rates between the two groups, patients with low eGFR less frequently experienced a relapse than those with normal eGFR. Walsh et al. previously reported risk factors for relapse of ANCA-associated vasculitis by analyzing 535 patients and found a strong association between worse renal function at initial presentation and lower risk of relapse [20]. They concluded that one of the reasons may be due to the state of immunosuppression caused by renal dysfunction. Although the immunosuppressive treatment was different from ours, our results may support their findings.

We propose two potential reasons for the worse-than-expected renal prognosis in our patients with normal eGFR at baseline. First, initial treatment was not intensified for patients without renal insufficiency at diagnosis, and 23 % of patients received only PSL without any immunosuppressive agents. On 3-year follow-up, we observed significantly higher eGFR in patients who received initial IVCY treatment than in those who did not. Further, the cumulative dose of IVCY treatment was significantly lower in patients without than in those with renal insufficiency, which might influence the results. Second, the rate of GPA diagnosis was higher in patients with normal eGFR than in those with low eGFR. Because renal involvement generally appears in the late phase of GPA, patients might not yet have manifested severe renal involvement at the time renal biopsy was performed. Furthermore, it is well known that patients with GPA have a more severe prognosis and more frequently flare than those with microscopic polyangiitis (MPA). This imbalance between GPA and MPA in the two groups might influence the results.

The present study is limited by its single-center, retrospective design, relatively short observational period, and small sample size. Therefore, significance might not have been reached due to the small sample size. A multi-center, prospective study is required to confirm our findings.

In conclusion, we found that damage accrual and renal outcomes do not significantly differ on 3-year follow-up in ANCA-associated crescentic glomerulonephritis patients with normal and low eGFR at diagnosis. Even when renal insufficiency was not observed at diagnosis, standard intensive treatment might still be required to prevent damage accrual.

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Compliance with ethical standards This study was approved by the Ethics Committee of Keio University. This study was a retrospective cohort using no samples other than those obtained for clinical use. In lieu of obtaining consent, public announcements of this study were posted.

Conflicts of interest H.H. received consulting fees from AstraZeneca. T.T. received grants from Abbott, Astellas, Bristol-Myers, Chugai, Daiichi Sankyo, Eisai, Mitsubishi Tanabe, Pfizer, Sanofi, Santen, Takeda, Teijin, AbbVie, Asahi Kasei, and Taisho Toyama; lecture fees from Abbott, Bristol-Myers, Chugai, Eisai, Janssen, Mitsubishi Tanabe, Pfizer, Takeda, Astellas, and Daiichi Sankyo; and consulting fees from AstraZeneca, Eli Lilly, Novartis, Mitsubishi Tanabe, Asahi Kasei, AbbVie, and Daiichi Sankyo.

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