
Renal outcome of kidney-transplantation in Korean recipients with ANCA-associated vasculitis

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ABSTRACT

Objectives. We investigated renal outcome of kidney-transplantation in Korean recipients with biopsy-proven renal involvement of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in a single centre.

Methods. We reviewed the medical records of 144 Korean patients and included 3 female patients with microscopic polyangiitis (MPA) and one male patient with eosinophilic granulomatosis with polyangiitis (EGPA) in this study. We obtained clinical and laboratory data related to kidney-transplantation, analysed renal outcome of kidney-transplantation in 4 recipients with AAV and compared it with those of previous studies.

Results. The mean age at diagnosis was 37.8 years and that at kidney-transplantation was 40.8 years. Time-gap from AAV to ESRD ranged from 1 to 48 months and that from AAV to kidney-transplantation ranged from 2 to 95 months. All kidney-recipients with had been followed-up for two years or greater. At diagnosis, MPO-ANCA was detected in only MPA patients, while, at transplantation, MPA-ANCA was detected in 2 MPA patients and an EGPA patient. All patients have received tacrolimus and mycophenolate mofetil based on glucocorticoid after kidney-transplantation. Among 4 kidney-recipients with AAV, one MPA patient underwent renal re-biopsies three times due to renal function deterioration during the follow-up. Renal histology revealed T cell-mediated and antibody-mediated rejection rather than relapse of MPA. Neither relapse nor graft failure was observed in our study.

Conclusion. Renal outcome of kidney-transplantation in recipients with AAV was good and kidney-transplantation is deserved to be recommend as a safe and effective therapeutic modality to AAV patients with ESRD.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic necrotising vasculitides, which mainly encroach small vessels from capillaries to arterioles (1). AAV generally consists of 3 variants based on clinical and histological features including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, identical to Wegener's granulomatosis) and eosinophilic GPA (EGPA, identical to Churg-Strauss syndrome) (1-5). The frequency of renal involvement of AAV depends on variants: 90–100% in MPA, 50–80% in GPA, 31–51% in ANCA positive EGPA and 4–16% ANCA negative EGPA (6). Most common histological feature of renal involvement of AAV is pauci-immune crescentic and/or necrotising glomerulonephritis, leading to rapid progressive glomerulonephritis (7). Renal involvement of AAV may result in end stage renal disease (ESRD) in 20-40% of AAV patients (8-10), and kidney transplantation has been considered a suitable therapeutic modality and more valuable benefits than maintenance of dialysis (11, 12). So far, histological features, age, glomerular filtration rate and PR3-ANCA at kidney transplantation were reported to be poor prognostic factors (13, 14). Despite a relatively low rate (0.02/patient year) of relapse of AAV after kidney-transplantation, because no guideline for kidney-transplantation in AAV patients with ESRD is recommended optimal timing and indication of kidney-transplantation and risk factors for relapse of AAV after kidney-transplantation, we still have concerns over the adverse effects of relapse on both graft- and patient-survival (8). Moreover, there was no report regarding renal outcome of kidney-transplantation in recipients with AAV in Korea. Hence, in this study, we investigated renal outcome of kidney-

Competing interests: none declared.

transplantation in Korean recipients with biopsy-proven renal involvement of AAV in a single centre.

Materials and methods

Patients

We retrospectively reviewed the details of the electrical medical records of 144 Korean patients according to the inclusion criteria as the follows: i) patients who were first classified as MPA, GPA or EGPA from October 2000 to July 2017 at Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance hospital; ii) those who were classified according to the 1990 American College of Rheumatology (ACR) classification criteria for GPA and EGPA, the 2007 European Medicines Agency (EMA) algorithm and the 2012 revised Chapel Hill Consensus Conference Nomenclature of Vasculitides (1-4); iii) those who had results of myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA at diagnosis and kidney-transplantation; vi) those who had biopsy-proven pauci-immune based crescentic and/or necrotising glomerulonephritis (7); v) those who had ESRD due to AAV, but not due to other meaningful medical conditions to accelerate progression to ESRD, such as diabetes mellitus, refractory hypertension, viral hepatitis, autoimmune diseases other than AAV; vi) those who underwent kidney-transplantation at Severance hospital after January 2005 and who had been followed-up for two years or greater; vii) those who had received prednisolone, mycophenolate mofetil and tacrolimus based on the same protocol suggested by Department of Transplantation Surgery after January 2005; viii) those who had well-written medical records at diagnosis, around kidney-transplantation and during the follow-up to identify clinical progress. Medical conditions were searched by the 10th revised International Classification of Diseases (ICD-10) and medications administered were monitored under the Korean Drug Utilization Review (DUR) system. Five patients fulfilled the inclusion criteria, but one patient had been followed-up for only two months. Finally, we included four patients in this

study and investigated renal outcome of kidney-transplantation in 4 Korean recipients with biopsy-proven AAV in a single centre. This study was approved by the institutional Review Board of Severance Hospital (4-2016-0901).

Clinical and laboratory data and AAV classification

We collected age at diagnosis and age at kidney-transplantation and gender as demographic data. We also collected time-gap from diagnosis of AAV to ESRD and time-gap from diagnosis of AAV to kidney-transplantation. We obtained the results of MPO-ANCA and PR3-ANCA not only at diagnosis, but also at kidney-transplantation. We also obtained renal histological features at diagnosis. We applied sequentially the 1990 ACR criteria for EGPA and GPA and the 2007 EMA algorithm modified by the 2012 CHCC definitions to study subjects as described in Table I (1-4).

Data related to kidney-transplantation

We reviewed the medical records related to kidney-transplantation regarding kidney donor, therapeutic regimens based glucocorticoid after kidney-transplantation, rejection, relapse of AAV, graft failure and CKD stage at present. Graft failure was defined as a status which needs to restart dialysis therapy or re-transplantation and death due to renal and non-renal cause (9, 15). Patients with unexplained elevated serum creatinine (greater than 30% increase over baseline), increased proteinuria (greater than 0.5g/day), and persistent haematuria (>5 RBC/HPF) were subjected to renal biopsy (7, 9, 16). Acute rejection was defined when histological features exhibited one of three characters: acute T cell-mediated rejection, acute antibody-mediated rejection and acute vascular rejection (17). Relapse was defined as recurrence or new onset of disease attributable to active vasculitis (18).

Literature review

We selected 4 studies with a considerable number of kidney-recipients with AAV from Western countries and case-reports from North-Eastern Asian countries with similar ethnicity to Ko-

rea, Japan and China. We also compared renal outcome between our study and previous studies.

Results

Baseline characteristics of 4 kidney-recipients with AAV classified by the 1990 ACR classification criteria and the 2007 EMA algorithm modified by the 2012 CHCC definitions

Our study included three female kidney-recipients with MPA and the mean age at diagnosis and that at kidney-transplantation were 43.7 year and 45.0 years. All MPA patients did not fulfil the 1990 ACR criteria for EGPA or GPA. All MPA patients exhibited pauci-immune crescentic and/or necrotising glomerulonephritis and had MPO-ANCA. Because they showed no granulomatosis on histology, or no GPA surrogate markers, they could be classified as MPA. Our study included only one male kidney-recipient with EGPA, who had been classified by the 1990 ACR classification criteria with items of asthma, eosinophilia, peripheral neuropathy, paranasal sinusitis and extravasation of eosinophils on histology. He had been diagnosed at 20 years of age and he underwent kidney-transplantation at 28 years of age. He had neither MPO-ANCA nor PR3-ANCA.

Renal outcome of kidney transplantation in 4 recipients with AAV

Renal outcome of 4 kidney-recipients with AAV is shown in Table II.

Time-gap from diagnosis of AAV to ESRD ranged from 1 to 48 months and that from diagnosis of AAV to kidney-transplantation ranged from 2 to 95 months. All kidney-recipients with AAV had been followed-up for two years or greater. On histology, two MPA patients exhibited pauci-immune crescentic and necrotising glomerulonephritis and one MPA patients exhibited pauci-immune crescentic glomerulonephritis. One EGPA patient exhibited extravasation of eosinophils along with pauci-immune crescentic glomerulonephritis. All patients received kidney from living related donor (LRD). MPO-ANCA was detected in all MPA patients at diagnosis, but it was

Table I. Baseline characteristics of 4 kidney-recipients with AAV classified by the 1990 ACR classification criteria and the 2007 EMA algorithm modified by the 2012 CHCC definitions.

Patients	Gender/ Age at diagnosis	Age at kidney transplantation	ANCA	ACR for EGPA	ACR for GPA	Histology compatible with 2012 revised CHCC GPA	Histology compatible with 2012 revised CHCC MPA and GPA surrogate markers	No histology GPA surrogate markers and PR3- or MPO- ANCA positivity	Clinical and histologic evidence of small-vessel vasculitis No GPA surrogate markers
1	F/33	33	MPO-ANCA	EGPA NO	GPA NO	GPA NO	GPA NO	GPA NO	MPA YES
2	F/40	41	MPO-ANCA	NO	NO	NO	NO	NO	YES
3	F/58	61	MPO-ANCA	NO	NO	NO	NO	NO	YES
4	M/20	28	ANCA negative	YES*					

*YES: asthma, sinusitis, eosinophilia and peripheral neuropathy; pauci-immune crescentic glomerulonephritis.

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; ACR: American College of Rheumatology; EMA: European Medicine Agency; CHCC: Chapel Hill Consensus Conference; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; PR3: proteinase 3; MPO: myeloperoxidase.

Table II. Renal outcome of kidney-transplantation in 4 recipients with AAV.

Patients (AAV variants)	Time-gap from AAV to ESRD (months)	Time-gap from AAV to kidney- transplantation (months)	Follow-up duration after kidney- transplantation (months)	Histological features	Kidney donor	ANCA at kidney- transplantation	Therapeutic regimens based on glucocorticoid after kidney- transplantation	Rejection	Relapse	Graft failure	Renal Function (CKD stage)
1 (MPA)	29	32	33	pauci-immune crescentic and necrotising glomerulonephritis	LRD	MPO-ANCA positive	tacrolimus and mycophenolate mofetil	NO	NO	NO	CKD I
2 (MPA)	1	2	28	pauci-immune crescentic glomerulonephritis with interstitial nephritis	LRD	MPO-ANCA positive	tacrolimus and mycophenolate mofetil	NO	NO	NO	CKD III
3 (MPA)	23	37	60	pauci-immune crescentic and necrotising glomerulonephritis	LRD	ANCA negative	tacrolimus and mycophenolate mofetil	YES	NO	NO	CKD IV
4 (EGPA)	48	95	126	pauci-immune crescentic glomerulonephritis extravasation of eosinophils	LRD	MPO-ANCA positive	tacrolimus and mycophenolate mofetil	NO	NO	NO	CKD I

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; ESRD: end stage renal disease; CKD: chronic kidney disease; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; LRD: living related donor; MPO: myeloperoxidase.

detected in only two of three MPA patients at kidney-transplantation. Meanwhile, MPO-ANCA was not detected in an EGPA patient at diagnosis, but it was detected at kidney-transplantation. All patients have received tacrolimus and mycophenolate mofetil based on glucocorticoid after kidney-transplantation according to the same protocol suggested by Department of Transplantation Surgery after January 2005. Among 4 kidney-recipients with AAV, one MPA patient exhibited the increased amount of proteinuria and the deterioration in renal function. Finally she underwent re-biopsy of kidney three times dur-

ing the follow-up. Renal histology by three re-biopsies revealed T cell-mediated and antibody-mediated rejection. Therefore, on the basis of histological features, we attributed the aetiology of aggravation of renal function to rejection rather than MPA. Plasmapheresis and glucocorticoid pulse therapy were performed for rapid kidney allograft dysfunction as induction therapy, and then tacrolimus and mycophenolate mofetil along with glucocorticoid were administered. Although three-time rejections provoked no graft failure, renal function deteriorated up to CKD stage IV though three-time rejections.

Literature reviews and comparison of renal outcome between this study and previous studies

We reviewed previous studies investigating renal outcome of kidney-transplantation in a large number of AAV patients described in Table III. A study with 113 kidney-recipients with AAV in the Netherlands reported the median time-gap from kidney-transplantation to relapse of AAV of 22 months, 5 year-graft-survival rate of 83% and 5 year-patient-survival of 95% (19). A study with 93 kidney-recipients with AAV in Australia and New Zealand reported that MPA showed the worse renal out-

Table III. Literature reviews and comparison of renal outcome between this study and previous studies.

Authors (reference number)	Nation	Number of kidney-recipients	Transplant years or age	Follow-up duration after KT (months)	Vasculitis relapse per patient year	Time-gap from KT to relapse (months)	Graft survival	Patient survival
Göçeroğlu A, et al. (17)	Netherlands	113	1984-2011	NA	NA	Median 22	95% at 1 year and 83% at 5 years	95% at 5 years
Tang et al. (18)	Australia and New Zealand	93	1996-2010	NA	NA		82% at 5 years and 50% at 10 years (MPA) 96% at 5 years and 62% at 10 years (GPA)	82% at 5 years and 68% at 10 years (MPA) 96% at 5 years and 85% at 10 years (GPA)
Geetha D, et al. (19)	USA	85	1996-2010	64	0.02	29.6 (2-55)	100% at 1 year, 97.9% at 5 years and 79% at 10 years	100% at 1 year, 93.4% at 5 years and 67.4% at 10 years
Little MA, et al. (20)	UK	107	1965-2005	66	0.01	NA	90% at 5 years and 70% at 10 years	90% at 5 years and 65% at 10 years
Kaseda K, et al. (22)	Japan	1	21 years	48	0		100%	100%
Tabata H, et al. (23)	Japan	1	57 years	NA	1	12	0%	100%
Sun Q, et al. (24)	China	1	2006	5	1	4 days after KT	100%	100%
Park ES, et al.	Republic of Korea	4	33, 41, 61 and 28 years	61.8	NA	NA	100%	100%

KT: kidney-transplantation; USA: United States of America; UK: United Kingdom; NA: not applicable; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis.

come than GPA in both graft-survival and patient-survival (50% at 10 years for MPA vs. 62% at 10 years for GPA, and 68% at 10 years for MPA vs. 85% at 10 years for GPA, respectively) (20). A study with 85 kidney-recipients with AAV in United States of America (USA) provided more concrete information on relapse of AAV represented as vasculitis relapse per patient year of 0.02 for the follow-up of 64 months and time-gap from kidney-transplantation to relapse of 29.6 months. Furthermore, it reported the better overall 10 year-graft survival than a study in Australia and New Zealand (79% vs. 50% for MPA and 62% for GPA), but similar 10 year-patient survival (21). Another study with 107 kidney-recipients with AAV in the United Kingdom (UK) provided the similar renal outcome to the results of a study conducted in USA including vasculitis relapse per patient year of 0.01 for the follow-up of 66 months, 10 year-graft survival of 70% and 10 year-patient survival of 65% (22).

There must be ethnic differences in both graft-survival and patient-survival between kidney-recipients with AAV in Western and North-Eastern Asian countries (23). However, as far as I know, there were only several case reports. Renal outcomes of kidney-transplantation in two Japanese kidney-recipients with AAV were reported. A 21 year-old

recipient exhibited neither relapse of AAV nor graft failure during the follow-up of 48 months, while a 57 year-old recipient showed relapse of AAV at 12 months after kidney-transplantation, leading to graft failure (24, 25). Renal outcome of kidney-transplantation in one Chinese recipient with AAV was also reported. This recipient immediately experienced relapse of AAV at 4 days after kidney-transplantation and underwent plasma exchange. Fortunately, despite relapse of AAV, no graft failure was observed during the follow-up of 5 months (26).

Our study included the more number of kidney-recipients and followed them up for the longer period than previous reports in Japan and China. Furthermore, renal outcome of kidney-transplantation was better than that of Japanese cases: neither relapse of AAV nor graft failure were observed during the follow-up of 61.8 months.

Discussion

In this study, we first reported renal outcome of kidney-transplantation in Korean recipients with biopsy-proven renal involvement of AAV in a single centre. Of 144 patients with AAV, 5 patients underwent kidney-transplantation due to ESRD related to AAV, but we included only 4 kidney-recipients with AAV, who had been followed-up

for two years or greater (3 MPA and 1 EGPA patients). Four patients exhibited a relatively long time-gap between diagnosis of AAV to ESRD of 25.3 months and that between diagnosis of AAV to kidney-transplantation of 41.5 months. During a considerable period of follow-up, one kidney-recipient underwent renal re-biopsy due to allograft rejection, but not relapses of MPA, on the basis of histopathological features of kidney tissues. We suggest that physicians should not hesitate to consider kidney-transplantation as one of renal replacement modalities in AAV patients, whose renal function deteriorates to ESRD, with concerns over relapse of AAV or graft failure.

A recent review described the discrepancies in clinical phenotypes and outcomes of AAV patients in Japan compared to those in the UK such as older at disease onset, less PR3-ANCA positivity, milder renal dysfunction and more frequent respiratory involvement (27).

Due to lack of data regarding renal outcome of kidney-transplantation in AAV recipients from North-Eastern Asian countries, we inevitably analysed renal outcome in those from Western countries and we learned several issues: first, relapse of AAV can occur regardless of the presence of graft failure (19, 21, 22). Thus, kidney-transplantation

is recommended to be performed after a sufficient period from the achievement of remission without a contraindication by ANCA positivity at kidney-transplantation (11). Relapse was more frequent in the first 2 years with differences in its frequency according variants: GPA (up to 60%), EGPA (35%) and MPA (8%) (10). Also cyclophosphamide or rituximab can be still necessary for treating post-transplant relapse of AAV despite immunosuppressive agents such as tacrolimus or mycophenolate mofetil based on glucocorticoids (11). Although, there was no relapse in our study, we realise the need for serial assessment of vasculitis activity and titres of ANCAs with a short-term follow-up schedule. Second, given that AAV recurrence was observed in small number of renal allografts (2%) (20), both reduced graft-survival and patient-survival rates mainly result from acute or chronic rejection, but not relapse of AAV. Third, MPA exhibits the rapider progression to graft failure (Hazard ratio 1.87) and the higher mortality (Hazard ratio of 1.94) than GPA at 10 years after kidney-transplantation (20). Returning to data from North-Eastern Asian countries, Japanese kidney-recipients with AAV exhibited graft-survival of 50%, while Chinese kidney-recipient with AAV exhibited graft-survival of 100%. However, because these reports included only one recipient per each case-report and two of three case-reports observed relapse of AAV and graft failure within 12 months. On the other hands, our study included 4 kidney-recipients among 144 AAV patients and observed renal outcome for at least more than 2 years. By contrast with studies from Western countries, our study showed no relapse, no graft failure and furthermore, no difference in graft-survival and patient-survival rates between MPA and EGPA. However, there were three cases of rejection in one patient with MPA. Thus, we conclude that kidney-transplantation is a safe and effective therapeutic method for AAV patients with ESRD under the administration of tacrolimus or mycophenolate mofetil based on glucocorticoids, which can provide therapeutic benefit for preventing relapse of MPA.

Cyclophosphamide or rituximab along with glucocorticoid are currently recommended as the induction therapeutic regimens (28-30). Once remission is achieved, azathioprine, methotrexate and mycophenolate mofetil and/or glucocorticoid are suggested as the maintenance therapeutic regimens (6, 31). On the other hands, the combination therapy of calcineurin inhibitors such as tacrolimus and sirolimus, and mycophenolate mofetil based on glucocorticoids, which has a selective mechanism for T and B cell post-transplantation immune modulation, has been recommended as post-transplantation maintenance therapeutic regimens until now (32). This combination therapy has increased both graft-survival and patient-survival rates, and reduced the opportunity of infection by (33). Furthermore a combination therapy of tacrolimus and mycophenolate mofetil and/or glucocorticoid, modulating both T and B cells, might be sufficient to maintain remission or low vasculitis activity after kidney-transplantation. Thus, we conclude that a combination therapy of tacrolimus and mycophenolate mofetil and/or glucocorticoid may reduce the rate of relapse of AAV, resulting in the low frequency of graft failure.

We wonder how we could affirm that the deterioration in renal function and three time-renal re-biopsies were due to allograft rejection rather than relapse of AAV in patient 3. We have two reasons beyond histological features: first, high titre of circulating ANCA at kidney-transplantation is associated with relapse of AAV during the follow-up after kidney-transplantation (22). Patient 3 exhibited ANCA positivity at diagnosis of AAV, however, ANCA negativity at kidney-transplantation. Thus, the possibility of relapse of AAV is relatively low. Second, patient 3 did not exhibit other extra-renal manifestations, which she had exhibited at diagnosis of AAV. Therefore, we affirm that patient 3 experience acute and chronic allograft rejection rather than relapse of AAV.

Our study has a strong merit that we first reported renal outcome of kidney-transplantation in recipients with AAV with a considerable follow-up duration after kidney-transplantation. Par-

ticularly, because all kidney-recipients received immunosuppressive drugs according to a controlled protocol in a single centre, we could minimise the confounding factors depending on therapeutic regimens. However, our study also has several issues. First, due to the limited number of kidney-recipients with AAV, the different follow-up duration as well as timing of kidney transplantation, our study could provide neither the general conclusion with statistical significance nor the right time to perform kidney transplantation after diagnosis. However, considering geographical and ethnic variations between Western and North-Eastern Asian countries, our study might have the clinical implication that it could provide a therapeutic potential of kidney transplantation in Korean AAV patients with ESRD including North-Eastern Asian countries. Second, due to the retrospective study-design, we could not provide the serial and protocol-based assessment of vasculitis activity and titres of ANCAs during the follow-up for the right timing of kidney transplantation to improve the graft survival. Last, because the kidney-recipients with AAV in our study were too heterogeneous to hypothesise the AAV variant-specific mechanism and furthermore no patients with GPA underwent kidney-transplantation, we could not elucidate renal outcome of kidney-recipients based on each variant of AAV. If future studies can prospectively and serially assess protocol-based vasculitis activity and titres of ANCAs, they could provide valuable and dynamic information of renal outcome of kidney-transplantation in recipients with AAV during the long-term follow-up. In conclusion, renal outcome of kidney-transplantation in recipients with AAV was good and kidney-transplantation is deserved to be recommend as a safe and effective therapeutic modality to AAV patients with ESRD.

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