Immunoadsorption Improves Remission Rates of Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitis and Severe Kidney Involvement

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Keywords
Immunoadsorption · Antineutrophil cytoplasmic antibody-associated vasculitis · Remission · End-stage kidney disease · Death

Abstract

Introduction: The role of plasma exchange in treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with severe kidney involvement is controversial. It is urgent to find effective treatments to improve prognosis of AAV patients. In this retrospective study, the outcomes of immunoadsorption (IA) onto protein A in AAV patients with severe kidney involvement were evaluated. Methods: Clinical data of 60 patients with AAV and severe kidney involvement were analyzed. Patients received cyclophosphamide or rituximab for remission induction, among which 16 were additionally treated with IA. Remission, end-stage kidney disease (ESKD), death, and relapse were compared. Results: Of 60 patients, 56 patients (93.3%) were positive for myeloperoxidase (MPO)-ANCA. At diagnosis, the estimated glomerular filtration rate and Birmingham Vasculitis Activity Score (BVAS) was 13.0 (7.7, 18.7) mL/min/1.73 m² and 11.1 ± 3.4, respectively. After 3–17 days (mean 10.4 days) of induction treatment, the disease activity decreased more obviously in the IA group (\(p = 0.022\)) than the control group. IA showed superior over standard regimen in clearance of MPO-ANCA within 3–31 days (median 11 days) after treatment (78.4% vs. 9.3%, \(p = 0.005\)). After a median follow-up of 20.2 months, remission was achieved more quickly (\(p = 0.035\)) and higher (hazard ratio (HR) = 2.3, 95% confidence interval (CI): 1.1–7.2, \(p = 0.033\)) in the IA group than the control group. IA therapy showed an advantage in reducing death (HR = 0.2, 95% CI: 0.1–0.9, \(p = 0.032\)). There was no difference in developing into ESKD in both groups (HR = 0.7, 95% CI: 0.3–2.0, \(p = 0.504\)). Multivariate Cox regression analysis indicated that early-stage remission was an independent predictor for ESKD (HR = 0.03, 95% CI: 0.003–0.25, \(p = 0.001\)) and death (HR = 0.07, 95% CI: 0.01–0.51, \(p = 0.009\)). Conclusion: IA treatment induces quicker and higher remission and lower mortality in AAV patients with severe kidney involvement. The early remission independently predicts the outcomes for these patients.

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a multisystem autoimmune disease characterized by inflammation of small- and medium-sized blood vessels and circulating autoantibodies to the leukocyte proteinase 3 or myeloperoxidase (MPO) [1–3]. AAV is prone to be present with severe kidney diseases and a clinical syndrome of rapidly progressive glomerulonephritis with poor prognosis [4, 5].

The therapy for AAV with kidney involvement has greatly improved in recent years. The use of cyclophosphamide (CYC) and/or rituximab (RTX) plus glucocorticoid (GC) effectively induces remission in the majority of cases [1, 6–14]. However, AAV patients with impaired renal function at diagnosis have a 5.42-fold increase in mortality compared with patients without kidney involvement [15]. A 5-year retrospective study showed that the cumulative renal survival rate at 5 years was only 50% for patients with end-stage renal failure [16]. Base on the pathogenesis of AAV, rapid removal of pathogenic autoantibodies and inflammatory mediators may potentially abolish the inciting cause of AAV and benefit patients [3, 17, 18]. The MEPEX trial showed that among AAV patients with serum creatinine (SCr) >500 μmol/L, the risk of progression to end-stage kidney disease (ESKD) was reduced by 24% at 1 year in patients with plasma exchange (PLEX) treatment [19]. Nevertheless, the long-term result of the MEPEX trial did not show any improvement in ESKD or death after a median follow-up of 3.95 years [20]. The PEXIVAS trial [21, 22] either had not observed any benefit of PLEX in AAV patients with the estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m² or alveolar hemorrhage. A retrospective study of AAV patients with an eGFR <30 mL/min/1.73 m² conducted at the Mayo Clinic showed similar results, consistent with the PEXIVAS trial [4]. Therefore, to identify effective approaches to improve outcomes of AAV patients with kidney involvement is urgently needed.

Immunoadsorption (IA) is a mature technique that specifically removes pathogenic antibodies without supplementation of plasma or albumin. IA theoretically avoids the loss of protective proteins and the risk of allergy and disease transmission due to transfusion of the blood product [23, 24]. Palmer et al. [25] found that IA combined with GC and CYC benefited AAV patients with rapidly progressive glomerulonephritis. After treatment, the titer of ANCA significantly decreased, and the renal function improved within 3–7 days. Esnault et al. [26] also reported that IA specifically cleared immunoglobulin (Ig) G (IgG) antibodies in 2 AAV patients and rapidly reduced the disease activity and induced remission. No observations have reported any serious side effects with IA treatment [25, 27].

However, controlled studies of IA in AAV patients with severe kidney diseases are still lacking. In this retrospective study, we evaluated whether additional IA therapy induced better outcomes than GC combined with immunosuppressant therapy alone.

Materials and Methods

Patients

In this single-center retrospective study, 179 patients meeting AAV vasculitis diagnostic criteria [28], older than 18 years in the Department of Nephrology at Tongji Hospital in Wuhan, China, from December 1, 2016, to January 20, 2020, were screened. Exclusion criteria were as follows: (1) maintenance hemodialysis >3 months; (2) disease course >12 months; (3) treated with PLEX or double-filtration plasmapheresis; (4) combined with other primary or secondary glomerular diseases, such as anti-glomerular basement membrane antibody glomerulonephritis and systemic lupus erythematosus; (5) with tumor; (6) lost to follow-up; and (7) the eGFR estimated by the CKD-EPI equation [29] >60 mL/min/1.73 m². Eventually, 60 patients, including 16 patients treated with additional IA and 44 patients treated with standard regimen, were included (online suppl. Fig. 1; see www.karger.com/doi/10.1159/000519608 for all online suppl. material). The date of starting treatment was registered to calculate the time-events outcome (Fig. 1). All patients were followed up to death or until January 20, 2021.

Treatment

According to patients’ conditions, patients received GC combined with CYC or RTX as induction remission therapy except for contraindications, such as severe infection. The dosage and reduction of oral GC depended on the attending physicians by referring to the initial standard of 1 mg/kg/day. Some patients received pulse methylprednisolone therapy, 500–1,000 mg/day for 3–5 days. CYC was given intravenously at 400–1,000 mg every month. RTX was given intravenously at 100 mg per month for 3 months, then 100 mg every 3 months. When CYC failed to induce remission, RTX was applied instead. Maintenance regimens, such as azathioprine (50–100 mg/day), mycophenolate mofetil (0.5–1.0 g/day), and leflunomide (5–10 mg/day), were determined by the physicians.

IA was performed by an adsorption column with genetic engineering recombinant protein A (KCI08, Guangzhou Koncen Bioscience Co., Ltd., Guangzhou, China) and perfusion apparatus (IF-800A, Jaftron Biomedical Co., Ltd., Zhubai, China) after separating the plasma and blood cells through a plasma separator (Plasmaflo-OP08W, Asahi Kasei Medical, Tokyo, Japan). IA was administered continuously or intermittently within 14 days. The 6,000 mL plasma volume was processed within 10 cycles per session. The frequency of IA treatments (no >10) was determined by changes in the ANCA titers, renal function, and the general conditions of patients and decided by the attending physicians.
**Clinical Assessment**

We obtained demographic data and laboratory examination data from the electronic medical record system. Birmingham Vasculitis Activity Score (BVAS) version 3 [30] was used to evaluate disease activity. The primary outcome was death from any cause, and the secondary outcomes were remission, ESKD, and relapse. ESKD was defined as permanent renal-replacement therapy, including peritoneal dialysis, hemodialysis, and kidney transplantation. Remission was defined as a BVAS of 0. Remission was defined as a BVAS of 0. ESKD, end-stage kidney disease; IA, immunoabsorption; BVAS, Birmingham Vasculitis Activity Score.

**Statistical Analysis**

Continuous variables were presented as mean ± SD if they were conforming to normal distribution or as the median (25th–75th percentile) if non-normal distribution. Categorical variables were presented as a count (percentage). For comparison of variables, the t test, Wilcoxon signed-rank test, Mann-Whitney U test, and \( \chi^2 \) test or Fisher’s exact test were appropriately used. Cumulative survival probabilities were calculated by the Kaplan-Meier method and were compared by the log-rank test between groups. Cox regression analysis was used to estimate the hazard ratios (HRs) and determine predictive factors for ESKD and death. Variables with \( p < 0.05 \) in univariate analysis were included in multivariate analysis. Patients with missing data were excluded in some specified analyses. We performed all statistical analyses using IBM SPSS Statistics version 26.0 software (IBM Corp., Chicago, IL, USA). A 2-tailed \( p < 0.05 \) was considered statistically significant.

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**Fig. 1.** Kaplan-Meier curves for remission (a), ESKD (b), death (c), and ESKD or death (d). There were 16 patients in the IA group and 44 patients in the control group. The log-rank test was used. The primary outcome was death from any cause. ESKD was defined as permanent renal-replacement therapy, including peritoneal dialysis, hemodialysis, and kidney transplantation. Remission was defined as a BVAS of 0. ESKD, end-stage kidney disease; IA, immunoabsorption; BVAS, Birmingham Vasculitis Activity Score.
Results

Baseline Characteristics

The baseline characteristics were shown in Table 1, all of p values >0.05. The median of age was 61.0 years, and 21 patients (35.0%) were female. The median of disease course, from the onset of clinical manifestations to the initiation of therapy, was 1.7 months. Fifty-six patients (93.3%) were positive for MPO-ANCA. The median of baseline SCr and eGFR was 367.0 μmol/L and 13.0 mL/min/1.73 m², respectively. Twenty-four patients (40.0%) had SCr ≥500 μmol/L or needed immediate hemodialysis. Only 5 patients received renal biopsy. All patients had high disease activity with a baseline BVAS of 11.1 ± 3.4.

| Clinical variables | All patients (N = 60) | IA group (N = 16) | Control group (N = 44) | p value |
|--------------------|-----------------------|-------------------|------------------------|---------|
| Age, year | 61.0 (53.3, 71.0) | 60.0 (40.3, 71.8) | 61.5 (53.3, 70.8) | 0.622<sup>a</sup> |
| Female, n (%) | 21 (35.0) | 3 (18.8) | 18 (40.9) | 0.112<sup>b</sup> |
| Disease course, months | 1.7 (1.0, 2.9) | 2.1 (1.1, 5.1) | 1.5 (0.9, 2.3) | 0.163<sup>a</sup> |
| Hypertension, n (%) | 19 (31.7) | 6 (37.5) | 13 (29.5) | 0.558<sup>b</sup> |
| MPO-ANCA subtype, n (%) | 56 (93.3) | 15 (93.8) | 41 (93.2) | 1.000<sup>b</sup> |
| WBC, ×10⁹/L | 7.7 (5.0, 10.4) | 9.0 (5.6, 11.4) | 7.3 (5.0, 10.2) | 0.394<sup>a</sup> |
| Hb, g/L | 76.0 (68.3, 86.8) | 72.5 (70.0, 87.0) | 78.5 (67.3, 86.0) | 0.861<sup>a</sup> |
| PLT, ×10⁹/L | 231.0±93.4 | 225.9±82.5 | 220.0±66.3 | 0.216<sup>c</sup> |
| Alb, g/L | 32.3±5.9 | 31.0±5.0 | 32.8±6.1 | 0.287<sup>b</sup> |
| Glb, g/L | 36.0±8.5 | 33.4±6.8 | 36.9±8.9 | 0.162<sup>b</sup> |
| SCr, μmol/L | 367.0 (249.0, 582.8) | 365.0 (183.5, 582.8) | 367.0 (277.8, 583.8) | 0.341<sup>a</sup> |
| SCr ≥500 μmol/L or immediate hemodialysis, n (%) | 24 (40.0) | 6 (37.5) | 18 (40.9) | 0.812<sup>b</sup> |
| EGFR, mL/min/1.73 m² | 13.0 (7.7, 18.1) | 14.4 (8.1, 43.6) | 12.0 (7.4, 17.6) | 0.210<sup>b</sup> |
| Proteinuria, g/24 h | 1.2 (0.6, 2.9) | 1.4 (0.3, 3.2) | 1.2 (0.6, 2.6) | 0.973<sup>b</sup> |
| ESR, mm/h<sup>d</sup> | 85.5 (58.8, 118.8) | 81.5 (29.8, 109.8) | 89.0 (61.8, 140.0) | 0.164<sup>a</sup> |
| BVAS | 11.1±3.4 | 11.3±3.6 | 11.0±3.3 | 0.736<sup>c</sup> |
| Hemoptyise, n (%) | 12 (20.0) | 6 (37.5) | 6 (13.6) | 0.066<sup>b</sup> |
| Organ involvement, n (%) | | | | |
| General | 27 (45.0) | 10 (62.5) | 17 (38.6) | 0.100<sup>b</sup> |
| Cutaneous | 1 (1.7) | 0 (0) | 1 (2.3) | 1.000<sup>b</sup> |
| Chest | 46 (76.7) | 12 (75.0) | 34 (77.3) | 1.000<sup>b</sup> |
| Renal | 60 (100) | 16 (100) | 44 (100) | – |
| Nervous system | 1 (1.7) | 1 (6.3) | 0 (0) | 0.267<sup>b</sup> |
| Induction therapy, n (%) | | | | |
| HIVMP | 21 (35.0) | 7 (43.8) | 14 (31.8) | 0.392<sup>b</sup> |
| GC + CYC | 43 (71.7) | 11 (68.8) | 32 (72.7) | 0.756<sup>b</sup> |
| GC + RTX | 5 (8.3) | 2 (12.5) | 3 (6.8) | 0.602<sup>b</sup> |
| GC + CYC + RTX | 4 (6.7) | 2 (12.5) | 2 (4.5) | 0.287<sup>b</sup> |
| Only GC | 8 (13.3) | 1 (6.3) | 7 (15.9) | 0.669<sup>b</sup> |
| Maintenance therapy, n (%)<sup>e</sup> | | | | |
| MMF | 11 (45.8) | 5 (50.0) | 6 (42.9) | 1.000<sup>b</sup> |
| AZA | 9 (37.5) | 4 (40.0) | 5 (35.7) | 1.000<sup>b</sup> |
| LEF | 3 (12.5) | 1 (10.0) | 2 (14.3) | 1.000<sup>b</sup> |
| CYC | 1 (4.2) | 1 (10.0) | 1 (7.1) | 1.000<sup>b</sup> |
| Follow-up time, months | 20.2 (9.7, 32.2) | 17.4 (14.3, 24.1) | 21.2 (3.8, 34.4) | 0.634<sup>a</sup> |

IA, immunoadsorption; MPO, myeloperoxidase; ANCA, antineutrophil cytoplasmic antibody; WBC, white blood cells; Hb, hemoglobin; PLT, platelet; Alb, albumin; Glb, globulin; SCr, serum creatinine; eGFR, estimation glomerular filtration rate; ESR, erythrocyte sedimentation rate; BVAS, Birmingham Vasculitis Activity Score; HIVMP, high-dose intravenous methylprednisolone; GC, glucocorticoid; CYC, cyclophosphamide; RTX, rituximab; MMF, mycophenolate mofetil; AZA, azathioprine; LEF, leflunomide; AAV, antineutrophil cytoplasmic antibody-associated vasculitis. <sup>a</sup>Mann-Whitney U test. <sup>b</sup>χ² test or Fisher’s exact test. <sup>c</sup>Independent sample t test. <sup>e</sup>The sample sizes of the IA group and control group were 16 and 38, respectively. <sup>®</sup>The sample sizes of remission in the IA group and control group were 10 and 14, respectively.
and at least 1 organ was involved. Chest involvement occurred in 46 patients (76.7%), and 12 patients (20.0%) presented with hemoptysis. The follow-up time was 20.2 (9.7, 32.2) months.

**ANCA, BVAS, Ig, and C**

The frequency of IA was 5.1 ± 1.8. Fifteen patients in the IA group and 13 patients in the control group were detected with MPO-ANCA by enzyme-linked immunosorbent assay before and within 1 month after treatment (3–31 days, median 11 days). The values of MPO-ANCA before treatment were 175.4 ± 82.2 RU/mL and 190.1 ± 38.8 RU/mL, respectively, in the IA group and control group (p = 0.559) (online suppl. Fig. 2a). Within 1 month after induction treatment, MPO-ANCA decreased significantly in both groups (online suppl. Fig. 2a). The values of MPO-ANCA decreased to 63.1 ± 72.2 RU/mL and 142.4 ± 75.7 RU/mL, respectively, in the IA group and control group (p = 0.010) (online suppl. Fig. 2a). The reduction rate of MPO-ANCA in the IA group versus control group (p = 0.005) (online suppl. Fig. 2b). In the first 6 months after treatment, the ANCA-positive percentage, detected by the indirect immunofluorescence assay, decreased gradually in both groups (online suppl. Fig. 2c). ANCA-positive percentage in the IA group versus control group was 100.0% versus 97.7% before treatment (p = 1.000), 68.8% versus 94.7% after 1 month treatment (p = 0.019), 46.7% versus 77.1% after 3-month treatment (p = 0.049), and 46.7% versus 58.1% after 6-month treatment (p = 0.538) (online suppl. Fig. 2c).

**BVAS, which reflected disease activity, decreased from 11.3 ± 3.6–6.3 ± 2.0, p < 0.001 and from 11.0 ± 3.3–8.6 ± 3.2, p < 0.001, respectively, in the IA group and control group (online suppl. Fig. 2d). The disease activity of IA group was lower than that of the control group after treatment (p = 0.022) (online suppl. Fig. 2d).

**Primary and Secondary Outcomes**

During follow-up, remission was achieved in 10 patients in the IA group and 14 patients in the control group. The cumulative remission rate in the IA group was higher than that in the control group (HR = 2.3, 95% CI: 1.1–7.2, p = 0.033) (Fig. 1a). Time to remission in the IA group and control group were 2.9 ± 1.2 months and 5.4 ± 4.0 months, respectively (p = 0.035). Cumulative remission rates at 6 months in the IA group and control group were 66.7% and 29.2%, respectively. Four patients in the IA group and 13 patients in the control group developed ESKD. There was no difference in the cumulative rate of ESKD in both groups (HR = 0.7, 95% CI: 0.3–2.0, p =

**Table 2. Cox regression analysis of risk factors predicting ESKD of AAV with severe kidney involvement**

| Variable                                      | Univariate analysis | Multivariate analysis |
|-----------------------------------------------|---------------------|----------------------|
|                                               | HR (95% CI)         | p value              |
| Age (years)                                   | 1.01 (0.98–1.04)    | 0.629                |
| Male                                          | 3.09 (0.89–10.81)   | 0.077                |
| Disease course (months)                       | 0.96 (0.78–1.17)    | 0.672                |
| Glb (g/L)                                     | 0.94 (0.89–1.00)    | **0.049**            |
| SCr ≥500 μmol/L or immediate hemodialysis     | 5.76 (2.01–16.53)   | **0.001**            |
|                                               |                     |                      |
| Proteinuria (g/24 h)                          | 0.99 (0.81–1.21)    | 0.891                |
| BVAS                                          | 1.28 (1.10–1.49)    | **0.001**            |
| Added IA treatment                            | 0.68 (0.22–2.11)    | 0.508                |
| Remission                                     | 0.04 (0.01–0.34)    | **0.003**            |

Bold values are significant. HR, hazard ratio; 95% CI, 95% confidence interval; Glb, globulin; SCr, serum creatinine; BVAS, Birmingham Vasculitis Activity Score; IA, immunoadsorption; AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ESKD, end-stage kidney disease.
0.504) (Fig. 1b). Twenty-three patients died, including 2 patients in the IA group and 21 patients in the control group during follow-up. A survival advantage was found in patients treated with IA compared with standard regimen (HR = 0.2, 95% CI: 0.1–0.9, p = 0.032) (Fig. 1c). Cumulative death rates at 12 months in the IA group and control group were 6.3% and 36.3%, respectively. When ESKD or death was identified as a composite endpoint, additional IA treatment was found to induce a better outcome (HR = 0.4, 95% CI: 0.2–0.9, p = 0.049) (Fig. 1d).

### Risk Factors for ESKD and Death

Univariate Cox regression analyses revealed the risk factors for ESKD (Table 2) and death (Table 3) in AAV patients with severe kidney involvement. Factors with p < 0.05 in the univariate analysis were selected for multivariate Cox regression analysis. Multivariate Cox regression models indicated that SCr ≥500 μmol/L or need for immediate hemodialysis at baseline (HR = 5.77, 95% CI: 1.61–20.72, p = 0.007), BVAS at baseline (HR = 1.19, 95% CI: 1.01–1.41, p = 0.043), and remission (HR = 0.03, 95% CI: 0.003–0.25, p = 0.001) were independent predictors for ESKD (Table 2). Age (HR = 1.08, 95% CI: 1.02–1.13, p = 0.004) and remission (HR = 0.07, 95% CI: 0.01–0.51, p = 0.009) were independent predictive factors for death (Table 3).

### Tolerance

IA treatment was well tolerated. Hypotension was observed during treatment in 4 patients in the IA group, which was corrected by supplementing albumin or saline and generally did not affect the treatment process. One patient presented with mild chest tightness during treatment and improved spontaneously. No allergy and other events were observed during treatment.

### GC, CYC, and Adverse Events

In patients who achieved remission by GC and CYC (IA group [N = 8], control group [N = 13]), steroids and immunosuppressors exposure levels and adverse events during follow-up were compared. When remission was achieved, the cumulative doses of GC and CYC in the IA group were lower than those in the control group, which were 3.6 (2.0, 4.6) g versus 4.7 (3.8, 6.7) g (p = 0.046) (online suppl. Fig. 4a) and 1.3 (0.8, 2.0) g versus 2.6 (1.7, 5.2) g (p = 0.026) (online suppl. Fig. 4b), respectively. After treatment, the daily doses of GC were tapered in both groups, and the doses in the IA group were less than those in the control group after 1-month, 3-month, and 6-month treatment (p = 0.049, 0.040, and 0.035), respectively (online suppl. Fig. 4c). However, there was no difference in both groups after treatment (p = 0.116) and after 12-month treatment (p = 0.590).

In these patients, infection that occurred at any site was the most common adverse event, occurring in 7 patients (87.5%) and 12 patients (92.3%) in the IA group and control group, respectively (p = 1.000) (online suppl. Table 1). The frequency of infection in the IA group ver-
Immunoadsorption Treatment in AAV with Severe Kidney Involvement

Discussion

AAV with an acute onset is an acute and critical disease, threatening the health of kidneys. PLEX has been advocated as an adjunct therapy in AAV with kidney involvement. However, the prospective PEXIVAS trial [22] and the retrospective study at the Mayo Clinic [4] did not find the benefit of PLEX in improving prognosis of AAV patients with severe kidney diseases. IA selectively removes pathogenic Igs and retains protective plasma proteins, theoretically presenting a therapeutic advantage over nonselective PLEX. Therefore, we conducted this retrospective study to evaluate the outcomes of IA therapy in AAV patients with severe kidney involvement.

We found that the disease activity decreased more obviously in the IA group than the control group after treatment. In terms of MPO-ANCA clearance, IA showed superior over standard regimen (78.4% vs. 9.3%) within 1 month after treatment. After IA treatment, the clearance rate of IgG (59.1 ± 28.7%) was higher than that of IgA (34.8 ± 17.9%) and IgM (35.5 ± 24.1%), and it was consistent with the changes of serum ANCA. The major isotype of ANCA is IgG, and this result well-reflected the characteristic of specific clearance of pathogenic antibodies by IA treatment, which was in line with previous reports [25–27]. We also found the superior ability of IA treatment in the decrease of C3 and C4. As the activation of the C system has been identified crucial for the development of AAV [2, 31], targeting the C system is a potential treatment strategy. It suggested that IA-related C clearance might also contribute to its renal protection.

We revealed that additional IA treatment induced quicker and higher remission. The majority of remission occurred in the first 6 months after treatment, in consistent with previous reports [4, 32, 33]. In the first 3 months, the ANCA-positive percentage was lower in the IA group than the control group. This indicated that the earlier negative turning of ANCA contributed to remission. However, our patients showed lower remission rates (control group, 44.5% and IA group, 66.9%) than that of previous studies from Western countries (70%–90%) treated with CYC and/or RTX [6]. The heterogeneity of race, disease activity, organ involvement, ANCA subtype, induction therapy, and the definition of remission might contribute to this difference. MPO-ANCA-positive vasculitis was dominant in Asian countries, such as Japan and China, with a positive percentage of 79%–93% [33, 34], such as that in our study. In a study from Chinese AAV patients treated with CYC, remission rate at 6 months was 47.1% [33], in line with that of our patients in the control group. Regarding a quicker and higher remission resulted from additional IA treatment, we should not only just be concerned about what was removed from patients but also what subsequent reaction happened in the body. It was reported that IA altered intracytoplasmic type 1 and type 2 T-cell cytokine productions [35]. A study about myasthenia gravis and Lambert-Eaton syndrome [36] demonstrated IA upregulated the anti-inflammatory factors (interleukin-10 [IL-10]) and reduce the pro-inflammatory factors (IL-17 and IL-18). Intravenous injection of purified staphylococcal protein A to healthy adult volunteers decreased peripheral lymphocyte counts as early as 8 h, peaked at 24 h, and returned to the baseline levels after 7 days [37]. Staphylococcal protein A was observed to bind to B cells in the splenic marginal zone inducing B-cell deletion [38–40]. Thus, apart from mechanically removing of toxic antibodies and Cs, IA might directly correct the impaired cellular and humoral immunity, which produce a more rapid response and higher clinical efficacy than those in the standard regimen.

We also found that added IA treatment reduced the occurrence of death. The cumulative death rate at 12 months was 36.3% in the control group, consistent with that of a study from Japan (28.9%) [41], but IA therapy decreased the death rate to 6.3% in our study. Anyway, the frequency of total deaths (38.3%, 23/60) is a little high in our cohort. The more severe pulmonary and kidney involvement may contribute to this difference. The causes of death were infections (52.2%), active vasculitis (26.1%), and others, in keeping with previous studies [42, 43]. Two patients in the IA group died of infections rather than active vasculitis, suggesting a significant improvement of disease activity by IA therapy. However, we did not find an advantage in renal survival and reducing relapse with IA therapy in the follow-up period. Histopathological differences, various maintenance regimens, insufficient follow-up time, and small sample size may have led to this result.
By multivariate Cox regression analysis, we found that the advantage of remission induced by IA treatment contributed to an improved prognosis. Remission was a significant independent ESKD-related and death-related predictor in AAV with severe kidney involvement. The Mayo Clinic’s study [4] also showed that remission at 6 months was a predictor for ESKD or death at 18 months. Due to the lack of uniform ANCA quantitative titers and IgG values in some patients, we analyzed the association of globulin with outcomes. Although univariate analysis revealed that globulin was associated with ESKD, multivariate analysis did not find the predictive value of globulin. Patients with SCr ≥500 μmol/L or who needed immediate hemodialysis and patients with high BVASs at baseline have an increased risk of ESKD. Increasing age was an independent risk factor for death. Various markers of renal impairment, disease activity, and advanced age have also been found to be associated with a worse prognosis in previous studies [32, 43, 44], which was consistent with our findings. In univariate analysis of factors predicting death, IA treatment was inversely associated with death.

Our study revealed no signs of intolerance during IA treatment. Hypotension was reported in a previous study [27] but did not lead to cessation of therapy. In our experience, adequate pre-flushing of the adsorption column prior to each session initiation to remove the protective fluid used to store the adsorbed column helped to prevent this undesirable side effect. In addition, chills, low-grade fever, musculoskeletal pain, nausea, and vomiting were also common adverse events of IA treatment [45], but none of these adverse events occurred in our observation. This may be due to the genetic engineering recombinant protein A column used in our study with a less toxic effect. Nevertheless, we should closely monitor the general situation of patients and deal with adverse events during the process of absorption.

Our study found that the advantage of earlier remission induced by IA treatment resulted in the reductions of steroids and immunosuppressor exposure doses. The infection frequency in the IA group was less than that in the control group in the first 6 months after treatment. However, there was no difference in infection frequency in the first 12 months after treatment and adverse events during follow-up. Thus, in the short term, reduced infections might also contribute to earlier remission in the IA group. But, it was not relying on reducing steroids and immunosuppressors exposure to improve the patients’ long-term outcome. Due to these results from the limited sample size, a further validation is needed in a prospective, large sample study.

There were some limitations in this study. First, the sample size in this study was relatively small, especially in the IA group. Second, as a retrospective study, some data were missing. For example, the lacking of lymphocytes subsets prevented the analysis of changes in the immune system. Third, due to the lack of renal biopsy samples from the majority of participants, histopathological differences could not be excluded. Fourth, treatment regimens were not predetermined, being prone to selection bias based on the disease severity. Fifth, the duration of follow-up is not long enough to determine the difference in the risk of ESKD and relapse. A prospective, multicenter, large-sample, randomized controlled trial is needed in the future. Despite these limitations, to our knowledge, this was the first controlled study which directly compared the efficacy of IA and the standard regimen in AAV patients with severe kidney involvement.

In conclusion, IA treatment induced quicker and higher remission in AAV patients with severe kidney involvement and reduced mortality. Remission was a significant independent predictor for ESKD and death. Thus, before a more promising strategy for remission induction appears, IA should be considered as an initial therapeutic choice for AAV patients with severe kidney involvement.

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Statement of Ethics
This study was reviewed and approved by the Ethics Committee of Tongji Hospital affiliated with the Tongji Medical College of Huazhong University of Science and Technology, approval number TJ-IRB20181107. Informed consent was obtained from all patients.

Conflict of Interest Statement
All the authors have nothing to disclose.

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Immunoadsorption Treatment in AAV with Severe Kidney Involvement

Author Contributions

Rui Zeng and Ying Yao contributed to the research idea and study design; Xiaoxin Chu, Yu Hong, YuXi Wang, Chong Yu, LiSheng Wang, Hui Tong, Jianjun Yan, Zhonghua Zhang, and Gang Xu contributed to data acquisition, analysis, or interpretation; Xiaoxin Chu performed statistical analysis and wrote the paper; and Rui Zeng and Ying Yao contributed to supervision or mentorship. Rui Zeng and Ying Yao contributed equally to this work. All the authors have critically reviewed the manuscript and approved the final version.

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Data Availability Statement

The data of this study are available from the corresponding au- thor on reasonable request.

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