Severe infections following rituximab treatment in antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Background: Severe infections were not rare in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients treated with rituximab. The current study aimed to evaluate severe infections in AAV patients received rituximab administration in a single Chinese center.

Methods: Twenty-seven patients were retrospectively included in this study. Their demographic and clinical data were analyzed. Severe infections were classified as grade ≥3 as proposed by the Common Terminology Criteria for Adverse Events V.4.0.

Results: Patients were followed up for 23.6±14.0 months from the time of rituximab initiation (mean rituximab dose 1270.4 mg). Ten severe infection events were recorded in 10 (37.0%) patients, corresponding to an event rate of 20.9 per 100 person-years. Pulmonary infections were the leading infectious complications (90%). Eight of the 10 infections occurred during the first 12 months of follow-up. In multivariable analysis, severe infection in the first year was independently associated with age (HR 1.121, 95% CI 1.011 to 1.243, P=0.031) and serum creatinine level (increased by per 88.4 μmol/L, HR 1.493, 95% CI 1.017 to 2.191, P=0.041).

Conclusions: In AAV patients receiving rituximab, severe infections were common even with the low-dose regimen. Pulmonary infections were the leading cause, and most infections occurred during the first 12 months of follow-up. Older age and renal dysfunction were the risk factors for infection.

Background

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiits (EGPA, previously known as Churg-Strauss syndrome) [1]. Left untreated, AAV is usually fatal, with a 1-year mortality rate of about 80% [2]. Immunosuppressive therapy, in particular corticosteroids and cyclophosphamide (CYC), was the cornerstone of remission-induction therapy and dramatically improved the outcome of AAV [3]. Although CYC induction regimens are effective, they are associated with high rates of adverse events, including leukopenia, severe infections, cancer, and gonadal toxicity [4, 5]. About 59% of deaths within the first 12 months were due to therapy-associated adverse events, mainly infections [6, 7]. The incidence of infection during induction therapy was 36.0% (41/114) in CYCLOPS study [5] and was 39.0% for glucocorticoids in combination with intravenous cyclophosphamide (IV-CYC) in a Chinese cohort [8].

Rituximab is an anti-CD20 monoclonal antibody resulting in B cell depletion. B-cells and ANCAs are implicated in the pathogenesis of AAV [9, 10]. In the last decade, rituximab treatment has been proved not inferior to CYC remission induction regimens and azathioprine (AZA) remission maintenance regimens, while the associated severe adverse events were not more frequent than CYC or AZA [11–15]. Rituximab is a promising therapy for the treatment of AAV and might be safer than cyclophosphamide regimens. In the treatment of membranous nephropathy, IgA nephropathy, and lupus nephritis, rituximab shows a

favorable safety profile and severe infections are uncommon [16–19]. But less optimistic data were reported in AAV patients. In RITUXIVAS study, infections occurred in 12 of the 33 patients in the rituximab group (36%) [11]. In MAINRITSAN study, severe infections developed in 19% patients in the rituximab group [13]. Recently, Kronbichler A, et al found that severe/life-threatening infections occurred in 25.52% AAV patients receiving rituximab therapy, with an event rate of 26.06 per 100 person-years [20]. These observations revealed that infections were still common in AAV patients receiving this new treatment regimen and should deserve careful attention. Baseline renal insufficiency was unremarkable in Kronbichler's study cohort [20]. In our center, a majority of AAV patients have renal involvement. In the current study, we aimed to evaluate severe infections in a group of AAV patients with high a proportion of renal dysfunction treated with rituximab and investigate potential risk factors.

Methods

Patients

AAV patients treated with rituximab in Peking University First Hospital between Dec 2010 and Aug 2018 were retrospectively recruited in this study. All patients met the Chapel Hill Consensus Conference criteria for AAV [1]. Exclusion criteria were defined as follows: (1) patients with secondary vasculitis such as propylthiouracil-induced AAV, or with comorbid renal diseases, for instance, anti-glomerular basement membrane disease, IgA nephropathy, lupus nephritis or diabetic nephropathy; (2) patients with negative ANCA. Follow-up began at the time of rituximab administration and ended on the date of last follow-up or the date of death. This research was conducted in accordance with the Declaration of Helsinki and was approved by the clinical research ethics committee of the Peking University First Hospital. Informed consent has been obtained from the patients (or their guardians).

Clinical data

All the clinical and laboratory data were respectively collected from medical records of the patients, including age, gender, diagnosis, date of diagnosis, date of rituximab administration, indication for the use of rituximab, cumulative doses of rituximab, ANCA serotype, disease phenotype, organ involvement, prior immunosuppressive therapies, concomitant treatment, laboratory values (serum creatinine, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), neutrophils, lymphocytes, hemoglobin, blood platelet count, CD4 + T cells, CD19 + B cells, immunoglobulins), Birmingham Vasculitis Activity Score (BVAS) [21], comorbidities (including chronic obstructive pulmonary disease (COPD), bronchiectasis, diabetes, hypertension, chronic heart failure), trimethoprim-sulfamethoxazole prophylaxis, response to treatment, presence of severe/life-threatening infections. The estimated glomerular filtration rate (eGFR) was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [22]. Patients with incomplete or missing medical records were excluded from further analysis.

Treatment

Treatment protocols were based on recommendations for AAV as described previously [11, 12, 15, 23], with modifications. In brief, rituximab could be used in induction therapy or maintenance therapy, or both. For induction therapy, a maximum weekly dose of 375 mg/m^2 was administered for 4 weeks, while for maintenance therapy, individually tailored rituximab regimens were applied. There might be prior immunosuppressive therapies in some patients, mainly glucocorticoids in combination with CYC for induction therapy and AZA for maintenance therapy. Patients with acute renal failure or pulmonary hemorrhage received 3 pulses of intravenous methylprednisolone (7–15 mg/kg/day) before the standard induction therapy. Patients with severe pulmonary hemorrhage or acute renal failure requiring dialysis at diagnosis received additional plasma exchanges.

Outcome and response to treatment

Presence of severe/life-threatening infections (grade ≥ 3) was defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 [24]. Response to treatment was classified as remission (complete remission or partial remission), treatment resistance and relapse, as previously described [25]. Other clinical outcome variables included death and dialysis-dependence.

Statistical analysis

Data were expressed as mean ± SD (for data that were normally distributed), or median and interquartile range (IQR; for data that were in skewed distribution) for continuous variables, and number (%) for categorical variables as appropriate. Quantitative parameters were compared using the Student's t-test (for data that were normally distributed) or the non-parametric test (for data that were in skewed distribution). Categorical variables were compared using the χ^2 test. Both univariable and multivariable Cox regression analysis were performed to test the association between candidate risk factors and severe/life-threatening infections. Demographic parameters (age, gender) and the variables showing significant association with the outcome in the univariable analysis were entered into a multivariable model. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 18.0 (Chicago, IL, USA).

Results

General data of the patients

Thirty-one AAV patients were treated with rituximab in Peking University First Hospital between Dec 2010 and Aug 2018, and eventually 27 of them were retrospectively recruited in this study. The detail for recruitment was showed in Figure 1. Among the 27 patients, 11 were male, 16 were female, with an age of 59.3±16.6 (range 26-82) years at rituximab administration. Eighteen, eight and one patients were classified as MPA, GPA and EGPA, respectively. Nineteen of the 27 (70.4%) patients were positive for MPO-ANCA, and 7 of the 27 (25.9%) patients were positive for PR3-ANCA, the remaining one (3.7%) was positive for both MPO-ANCA and PR3-ANCA. The initial serum creatinine and eGFR were 303.5±235.2 μmol/L and 32.5±31.5 mL/min/1.73m^2, respectively. Seven patients (25.9%) were on dialysis. The

average level of BVAS was 14.4±6.0 (range 3-29) at rituximab initiation. Twenty-six patients (96.3%) had renal involvement and 18/27 (66.7%) had pulmonary involvement. General data of total cohort and subgroups are shown in Table 1.

Treatment and outcomes

Median duration of AAV diagnosis to initiation of rituximab was 16 (range 0-143) months. Patients were followed for 23.6±14.0 months from the time of rituximab initiation (mean rituximab dose 1270.4 mg). Antibiotic prophylaxis with trimethoprim-sulfamethoxazole was administered in 7 out of 27 (25.9%). Treatment of the patients was depicted in Table 1 as well.

Ten patients (37.0%) presented with 10 infectious complications classified as CTCAE V.4.0 ≥3 (Figure 2 and Table 2). In detail, seven episodes were CTCAE V.4.0 grade 3 (6 pulmonary infections, 1 urinary infection), and 3 as grade 5 (3 pulmonary infections). None of the patients suffered ≥2 episodes of severe infections. The overall event rate was 20.9 per 100 person-years. Eight infections occurred during the first 12 months of follow-up, while the other 2 were observed after 42 and 43 months, respectively. Twenty-two (81.5%) patients achieved complete or partial remission of AAV. Ten patients (29.6%) were dialysis-dependent. Four patients (14.8%) died during the follow-up: 3 died of pneumonia and 1 of myocardial infarction.

Risk factors of severe infection

Since 80% of the infections occurred during the first year after rituximab administration, we aimed to identify factors predicting this risk. Univariable Cox regression analysis was performed for all parameters in Table 1. Age and serum creatinine were found to be associated with severe infection within the first year of follow-up. Since in Kronbichler's study [20], trimethoprim-sulfamethoxazole reduced the risk of severe infections, it was included into multivariable Cox regression model as well. All candidate parameters entered the multivariable analysis are shown in Table 3. In multivariable analysis, severe infection in the first year was independently associated with age (HR 1.121, 95% CI 1.011 to 1.243, P=0.031) and serum creatinine level (increased by per 88.4 μmol/L, HR 1.493, 95% CI 1.017 to 2.191, P=0.041).

Discussion

Since immunosuppressive therapy improved the outcome of AAV by reducing early death due to active disease, infections during follow-up have drawn increasing attention and remained a major issue in the management of AAV. Rituximab is a relatively new and effective treatment regimen for AAV. But severe infections were not rare in this subgroup of patients, and there seemed to be more infections than patients with other renal diseases [16–19] or rheumatic and musculoskeletal diseases (RMDs) [26] received rituximab administration. In RMDs patients, the event rate was 9.8 per 100 person-years [26], while in Kronbichler's study, severe infections occurred in 25.52% patients and the event rate was 26.06 per 100 person-years in AAV patients receiving rituximab therapy [20]. In general, patients with AAV may

have an increased risk of developing severe infections following rituximab therapy. Kidney involvement is quite common in AAV but renal dysfunction was unremarkable in Kronbichler's study cohort [20]. The majority of patients had renal insufficiency in our cohort, so the current study could further extend the previous results of this topic.

Although the dose of rituximab in our study was remarkably lower as compared with MAINRITSAN study (followed for 28 months, fixed rituximab dose 3000 mg) [13] and Kronbichler's study [20], severe infections were still very common, occurring in nearly 40% of the patients. Rituximab is an anti-CD20 monoclonal antibody resulting in B cell depletion. Recently, Salviani reported at the 19th International Vasculitis and ANCA Workshop that diagnosis of MPA and renal dysfunction significantly correlated to persistent B cell depletion after rituximab therapy [27]. There might be two reasons for the relatively high proportion of severe infection in our study. First, in China, there is a striking preponderance of MPA, constituting about 80% of patients with AAV [28]. Second, the majority of patients in the current study had renal insufficiency.

We found that pulmonary infections were the leading infectious complications (90%), which was consistent with previous studies [20, 29], and most infections occurred during the first 12 months of follow-up (80%), even within the first few months. Therefore, clinical manifestations and assessment of respiratory infection deserves more attention, especially during initial follow-up. Since most of the infections occurred during the first year after rituximab administration, we investigated the risk factors within this period. It was found that severe infection was independently associated with age and serum creatinine level. Older patients with renal insufficiency may benefit from a less intense rituximab treatment regimen, since they might be particularly vulnerable to severe infections, while they are more likely to have a very long-lasting B cell depletion.

To the best of our knowledge, this is first cohort study for infection complications after rituximab treatment in Chinese AAV patients, and the finding of association between renal function and severe infections further extended previous studies. However, there were several limitations of this study. First, since it was a retrospective study, data of continuous monitoring of B cells were incomplete, also the immunoglobulin levels at baseline and during follow-up. Second, only a few of the infectious cases had a positive microbial result.

Conclusions

In AAV patients receiving rituximab, severe infections were common even with the low-dose regimen. Pulmonary infections were the leading cause and most infections occurred during the first year of follow-up. Older age and renal dysfunction increase the risk.

Declarations

Ethics approval and consent to participate

This research was conducted in accordance with the Declaration of Helsinki and was approved by the clinical research ethics committee of the Peking University First Hospital (No. 2016010). Informed consent has been obtained from the patients (or their guardians).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Zhi-Ying Li contributed to study design, data analysis and article drafting. Min Chen and Ming-Hui Zhao contributed to study design and article revising. All the authors provided intellectual content of critical importance to the work and approved the manuscript.

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Abbreviations

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; AZA: azathioprine; BVAS: Birmingham Vasculitis Activity Score; COPD: chronic obstructive pulmonary disease; CRP: C reactive

protein; CTCAE: Common Terminology Criteria for Adverse Events; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear, nose and throat; ESR: erythrocyte sedimentation rate; GPA: granulomatosis with polyangiitis; IQR: interquartile range; IVMP: intravenous methylprednisolone; MPA: microscopic polyangiitis; WBC, white blood cell count.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1-11.
2. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis. 2003;41:776-84.
3. Adu D, Pall A, Luqmani RA, Richards NT, Howie AJ, Emery P, et al. Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. QJM. 1997;90:401-9.
4. Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, Cohen-Tervaert JW, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis. 2008;67:1004-10.
5. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150:670-80.
6. Little MA, Nightingale P, Verburgh CA, Hauser T, De Groot K, Savage C, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis. 2010;69:1036-43.
7. Lai QY, Ma TT, Li ZY, Chang DY, Zhao MH, Chen M. Predictors for mortality in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: a study of 398 Chinese patients. J Rheumatol. 2014;41:1849-55.
8. Yang L, Xie H, Liu Z, Chen Y, Wang J, Zhang H, et al. Risk factors for infectious complications of ANCA-associated vasculitis: a cohort study. BMC Nephrol. 2018;19:138.
9. Jennette JC, Xiao H, Falk RJ. Pathogenesis of vascular inflammation by anti-neutrophil cytoplasmic antibodies. J Am Soc Nephrol. 2006;17:1235-42.
10. Martin F, Chan AC. Pathogenic roles of B cells in human autoimmunity; insights from the clinic. Immunity. 2004;20:517-27.
11. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363:211-20.
12. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221-32.

13. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371:1771-80.
14. Terrier B, Pagnoux C, Perrodeau E, Karras A, Khouatra C, Aumaître O, et al. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. Ann Rheum Dis. 2018;77:1150-6.
15. Charles P, Terrier B, Perrodeau E, Cohen P, Faguer S, Huart A, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis. 2018;77:1143-9.
16. Dahan K, Debiec H, Plaisier E, Cachanado M, Rousseau A, Wakselman L, et al. Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. J Am Soc Nephrol. 2017;28:348-58.
17. Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, et al. A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction. J Am Soc Nephrol. 2017;28:1306-13.
18. Wang X, Cui Z, Zhang YM, Qu Z, Wang F, Meng LQ, et al. Rituximab for non-responsive idiopathic membranous nephropathy in a Chinese cohort. Nephrol Dial Transplant. 2018;33:1558-63.
19. Serris A, Amoura Z, Canoui-Poitrine F, Terrier B, Hachulla E, Costedoat-Chalumeau N, et al. Efficacy and safety of rituximab for systemic lupus erythematosus-associated immune cytopenias: A multicenter retrospective cohort study of 71 adults. Am J Hematol. 2018;93:424-9.
20. Kronbichler A, Kerschbaum J, Gopaluni S, Tieu J, Alberici F, Jones RB, et al. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2018;77:1440-7.
21. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM. 1994;87:671-8.
22. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-12.
23. Li ZY, Chang DY, Zhao MH, Chen M. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated vasculitis: a study of 439 cases in a single Chinese center. Arthritis Rheumatol. 2014;66:1920-6.
24. National Institutes of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. https://www.eortc.be › CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 10 Jan 2020.
25. Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2007;66:605-17.
26. Md Yusof MY, Vital EM, McElvenny DM, Hensor EMA, Das S, Dass S, et al. Predicting severe infection and effects of hypogammaglobulinaemia during therapy with rituximab in rheumatic and musculoskeletal diseases. Arthritis Rheumatol. 2019; 71:1812-23.

27. Chiara Salviani, Guido Jeannin, Giovanni Cancarini, Gina Gregorini. Factors influencing b cell repopulation after remission induction with rituximab in newly diagnosed, treatment-naïve patients with ANCA-associated vasculitis. Rheumatology 2019;58 Suppl 2:ii155.
28. Chen M, Yu F, Zhang Y, Zhao MH. Clinical and pathological characteristics of Chinese patients with antineutrophil cytoplasmic autoantibody associated systemic vasculitides: a study of 426 patients from a single centre. Postgrad Med J. 2005;81:723-7.
29. Cartin-Ceba R, Golbin JM, Keogh KA, Peikert T, Sánchez-Menéndez M, Ytterberg SR, et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. Arthritis Rheum. 2012;64:3770-8.

Tables

Table 1. Baseline characteristics of patients having severe infections versus those without severe infections

Parameters	total (n=27)	No severe infection (n=17)	Severe infection (n=10)	*P* values
Age, yr	59.3±16.6	53.9±15.0	68.5±16.0	0.025
Male, n (%)	11 (40.7%)	9 (52.9%)	2 (20%)	0.124
MPA/GPA/EGPA	18/8/1	10/6/1	8/2/0	0.635
MPO-ANCA/PR3-ANCA/Both	19/7/1	13/3/1	6/4/0	0.477
Organ involvement, n (%)				
Fever/fatigue/weight loss	23 (85.2%)	13 (76.5%)	10 (100%)	0.264
Kidney	26 (96.3%)	16 (94.1%)	10 (100%)	1.000
Pulmonary	18 (66.7%)	11 (64.7%)	7 (70%)	1.000
Joint pain	9 (33.3%)	5 (29.4%)	4 (40%)	0.683
Muscle pain	7 (25.9%)	4 (23.5%)	3 (30%)	1.000
ENT	7 (25.9%)	4 (23.5%)	3 (30%)	1.000
Serum creatinine, μmol/L	303.5±235.2	251.0±226.2	392.6±234.0	0.133
eGFR, ml/min/1.73m^2	32.5±31.5	41.2±33.8	17.8±21.5	0.061
CRP, mg/L	16.7 (5.5/35.8)	14.1 (5.4/30.0)	18.1(7.4/40.2)	0.672
ESR, mm/hr	51.3±38.4	46.9±39.3	59.1±37.6	0.458
BVAS	14.4±6.0	13.1±6.3	17.0±4.5	0.131
WBC, ×10^9/L	9.3±3.3	9.9±3.4	8.2±3.0	0.236
Neutrophils, ×10^9/L	7.0±3.1	7.8±2.6	5.6±3.5	0.088
Lymphocytes, ×10^9/L	1.0 (0.8/1.6)	1.2 (0.8/1.6)	0.9 (0.7/1.6)	0.396
Hemoglobin, g/L	9.8±1.9	10.3±2.1	8.9±0.8	0.060
Blood platelet count, ×10^9/L	19.8 (13.3/29.4)	21.1 (14.6/35.1)	16.6 (13.0/24.0)	0.367
CD4+ T cells, /μL	687.6±378.4	671.6±391.4	726.4±371.6	0.754
CD19+ B cells, /μL	202.9±134.9	186.4±130.6	242.9±147.2	0.363
IgG, g/L*	9.8±3.6			
IgA, g/L*	1.9±1.0			

IgM, g/L*	0.8±0.5			
Comorbidities (n)				
COPD	1 (3.7%)	0 (0%)	1 (10%)	0.370
Bronchiectasis	3 (11.1%)	2 (11.8%)	1 (10%)	1.000
Diabetes	3 (11.1%)	2 (11.8%)	1 (10%)	1.000
Hypertension	17 (63.0%)	10 (58.8%)	7 (70%)	0.692
Chronic heart failure	1 (3.7%)	1 (5.9%)	0 (0%)	1.000
Indication				
Relapse/refractory disease/1st line	12/8/7	9/6/2	3/2/5	0.107
Total rituximab dose	1270.4±905.9	1194.1±823.5	1400.0±1065.6	0.579
Rituximab infusions	2.6±1.4	2.5±1.3	2.8±1.7	0.641
Premedication (last 12 months)				
CYC (g)	3.0 (0/5.6)	3.0 (0.7/6.0)	0.5 (0/4.1)	0.223
Plasma exchange (ever)	16 (59.3%)	9 (52.9%)	7 (70%)	0.448
Pulsed IVMP	17 (63.0%)	12 (70.6%)	5 (50%)	0.415
Concurrently used medication				
Steroids	27 (100%)	17 (100%)	10 (100%)	
Trimethoprim–sulfamethoxazole	7 (25.9%)	3 (17.6%)	4 (40%)	0.365

*n (total)=17

[Abbreviations] BVAS: Birmingham Vasculitis Activity Score; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear, nose and throat; ESR: erythrocyte sedimentation rate; GPA: granulomatosis with polyangiitis; IVMP: intravenous methylprednisolone; MPA: microscopic polyangiitis; WBC, white blood cell count.

Table 2. Details of severe infection events

Parameters	n
Time to infection (m)	
≤3	4
4-6	1
7-12	3
13-36	0
36	2
CTCAE grade	
3	7
4	0
5	3
Infection sites	
Lower respiratory tract	9
Urinary tract	1

[Abbreviations] CTCAE: Common Terminology Criteria for Adverse Events.

Table 3. Analysis of risk factors for severe infection within 12 months after rituximab administration

Parameters	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* values	HR	95% CI	*P* values
Gender (male)	0.187	0.023 to 1.522	0.117	0.685	0.034 to 113.697	0.805
Age (years)	1.103	1.021 to 1.19	0.012	1.121	1.011 to 1.243	0.031
Serum creatinine (increased by per 88.4 μmol/L)	1.003	1.000 to 1.005	0.027	1.493	1.017 to 2.191	0.041
Trimethoprim–sulfamethoxazole	3.232	0.803 to 13.006	0.099	6.487	0.743 to 56.602	0.091

Figures

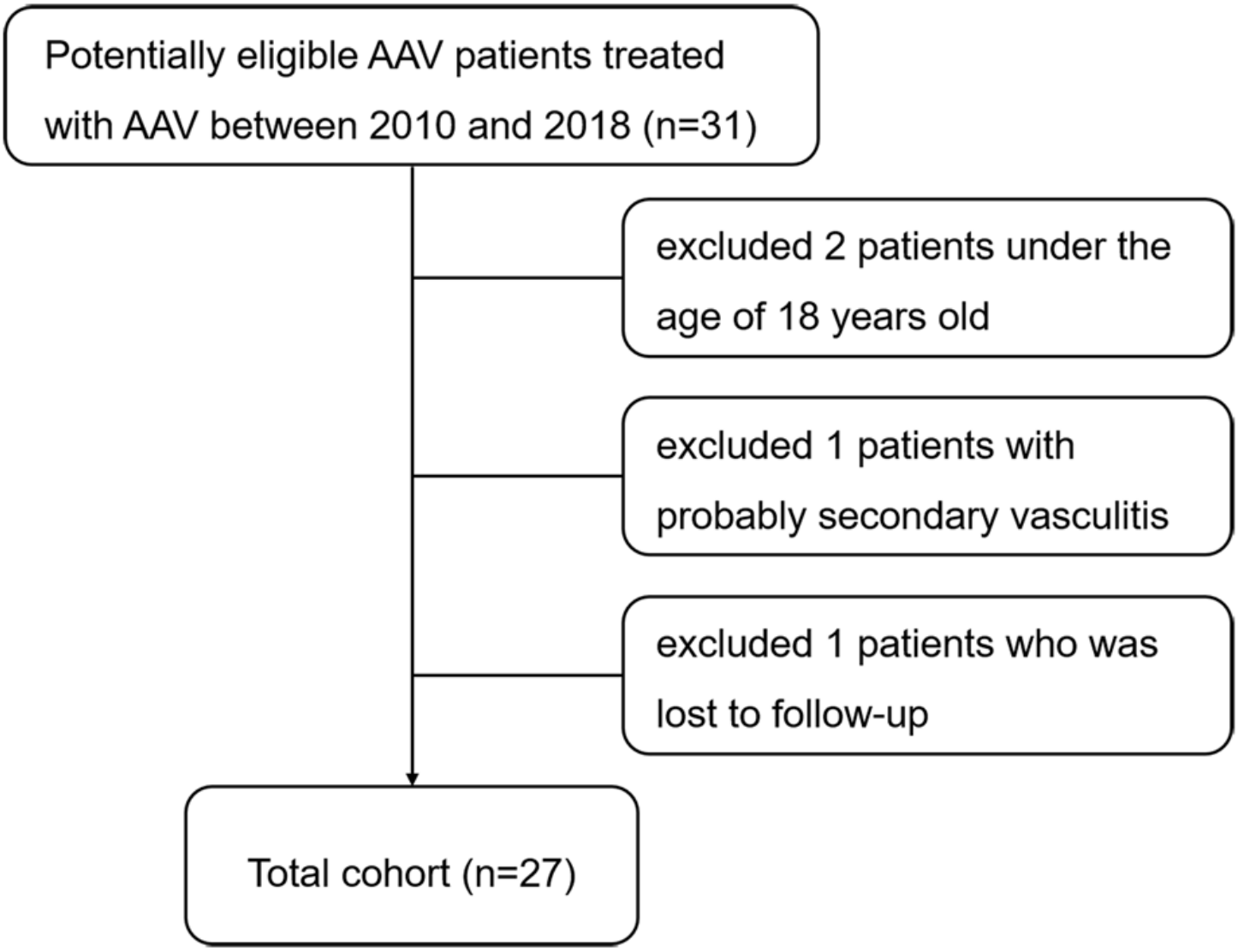

Figure 1

Flowsheet for recruitment

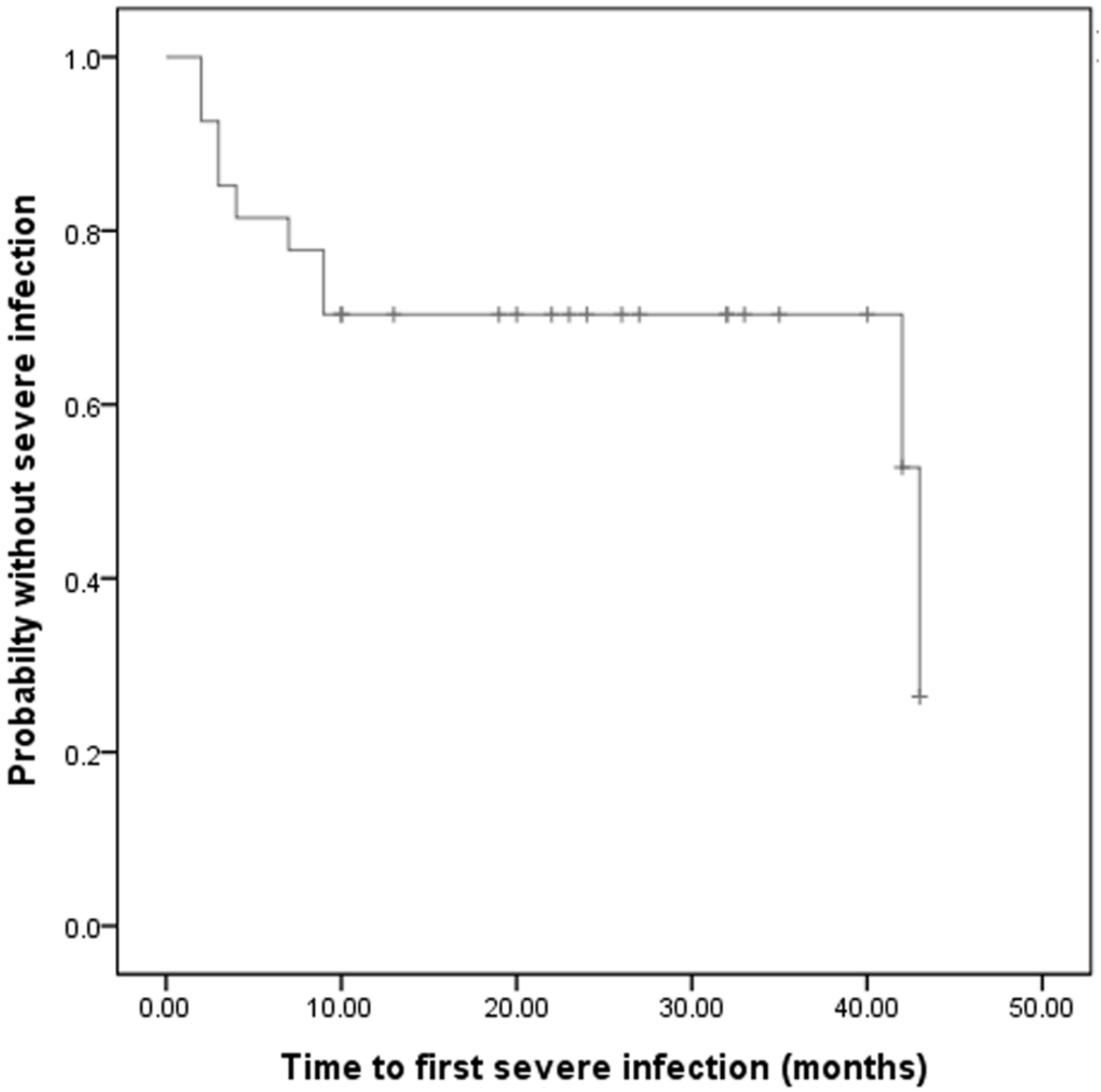

Figure 4

Kaplan-Meier curve of patients presenting with severe infections