Severe Infections following Rituximab Treatment in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

Zhi-Ying Li^{a-d} Min Chen^{a-d} Ming-Hui Zhao^{a-e}

^aRenal Division, Department of Medicine, Peking University First Hospital, Beijing, China; ^bPeking University Institute of Nephrology, Beijing, China; ^cKey Laboratory of Renal Disease, Ministry of Health of China, Beijing, China; ^dKey Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing, China; ^ePeking-Tsinghua Center for Life Sciences, Beijing, China

Keywords

Antineutrophil cytoplasmic antibody-associated vasculitis · Rituximab · Infection · Risk factors

Abstract

Introduction: 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 1,270.4 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: 1.011–1.243, $p = 0.031$) and serum creatinine level (increased by per 88.4 $\mu\text{mol/L}$; HR: 1.493, 95% CI: 1.017–2.191, $p = 0.041$). **Conclusion:** 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.

© 2020 The Author(s)

Published by S. Karger AG, Basel

Introduction

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 polyangiitis (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 the 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]. However, less optimistic data were reported in AAV patients. In the RITUXIVAS study, infections occurred in 12 of the 33 patients in the rituximab group (36%) [11]. In the MAINRITSAN study, severe infections developed in 19% patients in the rituximab group [13]. Recently, Kronbichler et al. [20] 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. 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.

Material and Methods

Patients

AAV patients treated with rituximab in Peking University First Hospital between December 2010 and August 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 (No. 2019yan217). Written 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 and corticosteroids, 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, and immunoglobulins), Birmingham Vasculitis Activity Score (BVAS) [21], comorbidities (including chronic obstructive pulmonary disease [COPD], bronchiectasis, diabetes, hypertension, and chronic heart failure), usage of prophylactic antibiotics, response to treatment, presence of severe/life-threatening infections, and spectrum of causative organisms. The estimated glomerular filtration rate (eGFR) was calculated by the 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/m² 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 cyclophosphamide for induction therapy and azathioprine (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 $\pm$ 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 Student's *t* test (for data that were normally distributed) or the nonparametric test (for data that were in skewed distribution). Categorical variables were compared using the χ^2 test. Both univariable and multivariable Cox regression analyses were performed to test the association between candidate risk factors and severe/life-threatening infections. Demographic parameters (age and 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 December 2010 and August 2018, and eventually, 27 of them were retrospectively recruited in this study. The detail for recruitment is shown in Figure 1. Among the 27 patients, 11 were male and 16 were female, with an age of 59.3 ± 16.6 (range 26–82) years at rituximab administration. Eighteen, 8, and 1 patients were classified as MPA, GPA, and EGPA, respectively. Nineteen of the 27 (70.4%) patients were positive for MPO-ANCA, 7 of the 27 (25.9%) patients were positive for PR3-ANCA, and the remaining 1 (3.7%) was positive for both MPO-ANCA and PR3-ANCA. The initial serum creatinine and eGFR were 303.5 ± 235.2 $\mu\text{mol/L}$ and 32.5 ± 31.5 mL/min/1.73 m^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

The 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 1,270.4 mg). Antibiotic prophylaxis with trimethoprim-sulfamethoxazole was administered in 7 out of 27 (25.9%). Treatment of the patients is depicted in Table 1 as well.

Ten patients (37.0%) presented with 10 infectious complications classified as CTCAE V.4.0 ≥ 3 (Fig. 2; Ta-

Fig. 1. Flow sheet for recruitment.

ble 2). In detail, 7 episodes were of CTCAE V.4.0 grade 3 (6 pulmonary infections and 1 urinary infection) and 3 were of grade 5 (3 pulmonary infections). The spectrum of causative organisms is listed in Table 2 as well. 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, while 5 patients were resistant to therapy. Relapse occurred in 3 cases during follow-up. 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 the multivariable Cox regression model as well. All candidate parameters included in 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: 1.011–1.243, $p = 0.031$) and serum creatinine level (increased by per 88.4 $\mu\text{mol/L}$; HR: 1.493, 95% CI: 1.017–2.191, $p = 0.041$).

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, years	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/1.73 m 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/1 h	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 ^a	9.8±3.6			
IgA, g/L ^a	1.9±1.0			
IgM, g/L ^a	0.8±0.5			
Trough WBC after rituximab therapy, ×10 ⁹ /L	4.3 (2.8/6)	4.3 (3.0/6.7)	4.3 (1.8/5.4)	0.203
WBC at the onset of infection, ×10 ⁹ /L			8.5±5.9	
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	1,270.4±905.9	1,194.1±823.5	1,400.0±1,065.6	0.579
Rituximab infusions	2.6±1.4	2.5±1.3	2.8±1.7	0.641
Prednisone or equivalent dose				
Cumulative, g	13.4±7.6	15.6±7.8	10.0±6.6	0.091
At the time of infection, mg/day			16.2 (7.5/30)	
Previous IS, n (%)				
CYC	20 (74.1)	14 (82.4)	6 (60.0)	0.365
Others	7 (25.9)	6 (35.5)	1 (10)	0.204
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), n (%)	16 (59.3)	9 (52.9)	7 (70)	0.448
Pulsed IVMP, n (%)	17 (63.0)	12 (70.6)	5 (50)	0.415
Concurrently used medication, n (%)				
Steroids	27 (100)	17 (100)	10 (100)	
Concomitant IS, n (%)				
MMF	1 (3.7)	1 (5.9)	0	
Prophylactic trimethoprim-sulfamethoxazole	7 (25.9)	3 (17.6)	4 (40)	0.365

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; IS, immunosuppressants; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; WBC, white blood cell count. ^a n (total) = 17.

Table 2. Details of severe infection events

Parameters	<i>n</i>
Time to infection, months	
≤3	4
4–6	1
7–12	3
13–36	0
>36	2
CTCAE grade	
3	7
4	0
5	3
Infection sites and spectrum of causative organisms	
Lower respiratory tract	9
PCP and fungi	2
MSSA	1
MRSA	1
Tuberculosis	1
Virus	1
Unidentified	3
Urinary tract	1
Unidentified	1

CTCAE, Common Terminology Criteria for Adverse Events; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PCP, pneumocystis pneumonia.

Fig. 2. Kaplan-Meier curve of patients presenting with severe infections.

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. However, 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 RMD 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 the MAINRITSAN study (followed for 28 months, fixed rituximab dose 3,000 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 et al. [27] 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. There might be 2 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 deserve more attention, especially during initial follow-up. Since most of the infections occurred during the first year after rituximab administration, we inves-

Table 3. Univariable and multivariable analysis of risk factors for severe infection within 12 months after rituximab administration

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

tigated 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 the 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 6 of the infectious cases had a positive microbial result.

In conclusion, 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 increased the risk.

References

- 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 Jan;65(1):1–11.
- 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 Apr;41(4):776–84.
- 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 Jun;90(6):401–9.
- 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 Jul;67(7):1004–10.
- 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 May 19;150(10):670–80.

Statement of Ethics

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. 2019yan217). Written informed consent has been obtained from the patients (or their guardians).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by a grant from National Key Research and Development Program (No. 2016YFC0906102), two grants from the National Natural Science Fund (Nos. 81870477 and 81870478), a grant from the Capital's Funds for Health Improvement and Research (No. 2020-2-4073), and a grant from the Scientific Research Seed Fund of Peking University First Hospital (No. 2018SF004).

Author 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.

- 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 Jun;69(6):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 Sep;41(9):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 Jun;19(1):138.
- 9 Jennette JC, Xiao H, Falk RJ. Pathogenesis of vascular inflammation by anti-neutrophil cytoplasmic antibodies. *J Am Soc Nephrol*. 2006 May;17(5):1235–42.
- 10 Martin F, Chan AC. Pathogenic roles of B cells in human autoimmunity: insights from the clinic. *Immunity*. 2004 May;20(5):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 Jul 15;363(3):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 Jul;363(3):221–32.
- 13 Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med*. 2014 Nov;371(19):1771–80.
- 14 Terrier B, Pagnoux C, Perrodeau É, Karras A, Khouatra C, Aumaitre O, et al. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheum Dis*. 2018 Aug;77(8):1150–6.
- 15 Charles P, Terrier B, Perrodeau É, 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 Aug;77(8):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 Jan;28(1):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 Apr;28(4):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 Sep;33(9):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 Mar;93(3):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 Oct;77(10):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 Nov;87(11):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 May;150(9):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 Jul;66(7):1920–6.
- 24 National Institutes of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
- 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 May;66(5):605–17.
- 26 Md Yusof MY, Vital EM, McElvenny DM, Hensor EMA, Das S, Dass S, et al. Predicting severe infection and effects of hypogammaglobulinemia during therapy with rituximab in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol*. 2019 Nov;71(11):1812–23.
- 27 Salviani C, Jeannin G, Cancarini G, Gregorini G. Factors influencing B cell repopulation after remission induction with rituximab in newly diagnosed, treatment-naïve patients with ANCA-associated vasculitis. *Rheumatology*. 2019 Mar;58(Suppl 2):ii155.
- 28 Chen M, Yu F, Zhang Y, Zhao MH. Clinical [corrected] 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 Nov;81(961):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 Nov;64(11):3770–8.