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Pneumocystis jirovecii Pneumonia Prophylaxis in Patients with ANCA Vasculitis on Rituximab Maintenance Therapy

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Keywords
ANCA vasculitis · Rituximab · *Pneumocystis jirovecii* · Prophylaxis · Treatment

Abstract
Introduction: Although an increased risk of *Pneumocystis jirovecii* pneumonia (PJP) has been reported in adults receiving rituximab for induction therapy, current evidence is lacking on the utility of PJP prophylaxis in ANCA-associated vasculitis (AAV) patients on maintenance rituximab therapy. The purpose of this study was to compare the incidence of PJP pneumonia and the outcomes of AAV patients with and without PJP prophylaxis. ***Methods:*** We performed an observational, single-center, retrospective study examining patients with AAV in clinical remission and on rituximab maintenance therapy. We divided the patients into two groups: those with and without PJP prophylaxis. We explored factors associated with PJP prophylaxis use. We additionally looked at several outcomes, including PJP infections, infections requiring hospitalizations, end-stage kidney disease (ESKD), and death. Data were analyzed using *T* test, Fisher's exact test, univariate, and multivariate logistic regression as appropriate. ***Results:*** A total of 129 patients with mean follow-up time of 7.2 (5.4) years were included: 44% received PJP prophylaxis and 56% of patients did not. There were no PJP infections in the entire cohort. Lung involvement was associated with increased odds of prescribing PJP prophylaxis (OR: 4.09 [95% CI: 1.8–9.82]). PJP prophylaxis did not decrease infection rates requiring hospitalizations, ESKD, or death. Glucocorticoid use, however, was associated with increased rates of infections requiring hospitalizations (OR: 5.54 [95% CI: 2.01–15.4]) and death (OR: 4.67 [95% CI: 1.36–15.71]) even after adjustment for age, gender, and use of PJP prophylaxis. ***Conclusion:*** Regardless of the use of PJP prophylaxis during the maintenance phase of AAV management, PJP pneumonia was not observed. AAV patients with lung involvement were more likely to be on PJP prophylaxis.

Introduction

Rituximab, a chimeric monoclonal antibody targeting CD20-expressing B cells, is a standard therapy used in the induction and maintenance phases of ANCA-associated vasculitis (AAV) [1–4]. Secondary hypogammaglobulinemia and increased risk of infections due to prolonged B cell depletion, lasting around 6–9 months with rituximab monotherapy, pose a significant challenge in the care of AAV patients [5, 6]. T cells are not affected directly by rituximab, and

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therefore, opportunistic infections rarely occur. In AAV patients receiving rituximab, evaluating the risk and types of infections is challenging due to the concomitant use of high-dose steroids, particularly during the initial induction phase of treatment.

Pneumocystis jirovecii is an opportunistic fungal pathogen that can cause severe *Pneumocystis jirovecii* pneumonia (PJP) and significant mortality in patients with defective cell-mediated immunity. PJP prophylaxis is recommended in patients receiving moderate to high-dose glucocorticoid treatment (≥20 mg/day of prednisone or equivalent for greater than a month) who have an additional cause of immunodeficiency, such as underlying malignancy or concomitant use of immunosuppression. In patients with rheumatological diseases, guidelines for PJP prophylaxis are not well established [7]. Recently, Park et al. [8] concluded that in individuals with rheumatological diseases and receiving a high dose of prednisone (≥30 mg/day of prednisone or equivalent) within 4 weeks of rituximab administration, the benefits of PJP prophylaxis outweighed the risks. However, it is unclear if this applies to AAV patients as they comprised only 22% of their patient population. A recent study focused on AAV patients on rituximab maintenance therapy (n = 709) and found 5 cases of PJP, highlighting the lower rates of PJP infections than previously observed [9]. Given the paucity of data on PJP prophylaxis in AAV patients treated with rituximab for remission maintenance, we aimed to retrospectively investigate the use of PJP prophylaxis in adult patients with AAV receiving rituximab maintenance therapy with no to small doses of glucocorticoids in a single university medical center and evaluate severe outcomes including PJP infections, infections requiring hospitalizations, and end-stage kidney disease (ESKD).

Methods

Adult patients diagnosed with AAV between 2009 and 2023 were identified from the Johns Hopkins Vasculitis Center database and included in the study. All patients had to have a clinical diagnosis of AAV based on the 2012 Chapel Hill Consensus Conference definitions for AAV [10]. For inclusion in this study, patients were required to be in clinical remission and in the maintenance phase of treatment. Clinical remission was defined by the treating physician as having no signs or symptoms of vasculitis activity. All patients had to receive at least one dose of maintenance rituximab therapy. The first dose of rituximab maintenance therapy reflected the start of the maintenance phase. The dose and frequency of rituximab was at the discretion of the treating physician but was between 500 mg and 1,000 mg, and either at a fixed dose every 6 months or as a tailored regimen. Additionally, patients were required to be on less than or equal to 10 mg/day prednisone. Patients who received immunosuppressive agents other than rituximab and prednisone and those

Table 1. Demographic and clinical characteristics of all patients

Baseline characteristics	n = 129
Age, years	62.5 (16)
Follow-up time, years	7.2 (5.4)
Gender	
Male	51 (40)
Female	78 (60)
Race	
Caucasian	102 (79)
African American	13 (10)
Hispanic	7 (5)
Asian	5 (4)
Others	2 (1)
ANCA type	
PR3	68 (53)
MPO	56 (43)
PR3 + MPO	2 (1.5)
Negative	2 (1.5)
Unknown	1 (1)
Disease type	
GPA	76 (59)
MPA	48 (37)
eGPA	5 (4)
Prior induction treatment	
Rituximab	124 (96)
Cyclophosphamide	50 (39)
Methotrexate	14 (11)
Plasma exchange	4 (3)
Leflunomide	3 (2)
Cyclosporine	1 (1)
Infliximab	1 (1)
Azathioprine	2 (2)
Adalimumab	1 (1)
Etanercept	1 (1)
PJP prophylaxis	
Yes	57 (44)
No	72 (56)
Chemoprophylaxis	
Trimethoprim-sulfamethoxazole	40 (70)
Dapsone	9 (16)
Atovaquone	8 (14)

PR3, proteinase-3; MPO, myeloperoxidase; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; eGPA, eosinophilic granulomatosis with polyangiitis, ANCA, anti-neutrophil cytoplasmic antibody; PJP, *Pneumocystis jirovecii* pneumonia. Numeric continuous values are presented as mean (±SD) and categorical variables as n (%).

with concomitant anti-glomerular basement membrane (anti-GBM) disease or dual positivity for both ANCA and anti-GBM antibodies were excluded. Patients who had a clinical relapse, defined by new signs or symptoms of vasculitis activity requiring escalation of immunosuppression, were excluded from the study. Data were collected retrospectively using electronic medical health records.

Demographics and baseline disease characteristics including age, race, gender, duration of disease, clinical manifestations, ANCA type, disease type, organ involvement were included. Organ involvement was ascertained by the treating physician using electronic medical records. Details of maintenance rituximab immunosuppression, prednisone dose, PJP prophylaxis medications, serum immunoglobulin G (IgG) levels, and CD4 count were extracted. Prednisone dose was extracted from the last follow-up appointment. Hypogammaglobulinemia was defined as a serum IgG level less than 500 mg/dL and a low CD4 count was defined as <200 cells per cubic millimeter. We evaluated several clinical outcomes including PJP infections, infections requiring hospitalizations, death, and ESKD. Having a diagnosis of a PJP infection required the identification of organisms in sputum or bronchoalveolar lavage fluid. ESKD was defined as the need for continuation of renal replacement therapy in the form of dialysis for at least 3 months or the receipt of kidney transplantation.

Baseline summary statistics were calculated using median (interquartile range) and mean (standard deviation (SD)). Outcomes were analyzed using *T* test, Fisher's exact test, univariate, and multivariate logistic regression as appropriate. Two-tailed p values of ≤0.05 were considered significant. Analyses were performed using R Core Team, Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the Institutional Review Board at Johns Hopkins University School of Medicine.

Results

A total of 129 patients were included. The mean (SD) age was 62.5 (16) years old and the mean (SD) follow-up was 7.2 (5.4) years. There were 78 (60%) females. One hundred two (79%) patients were Caucasian and 13 (10%) African American. Sixty-eight (52%) had PR3 ANCA and 56 (53%) had MPO ANCA. Forty-five patients (35%) had relapsing disease. Prior induction therapies are listed in Table 1. During the maintenance treatment period, 57 (44%) patients received PJP prophylaxis, whereas 72 (56%) did not. CD4 level was checked in 91 (71%) patients and serum IgG level was checked in 111 (86%) patients (Table 1).

In the PJP prophylaxis group, the mean (SD) duration of rituximab therapy was 3.6 (2.5) years, whereas in patients who did not receive PJP prophylaxis, the mean (SD) duration of rituximab therapy was 3.1 (2.1) years. Details of prednisone dose, CD4 count, and serum IgG level are listed in (Table 2).

Adjusting for age, race, gender, and prednisone use, lung involvement was associated with increased odds of prescribing PJP prophylaxis (OR: 4.09 [95% CI: 1.8–9.82]). CD4 count <200 cells/mm^3 (n = 5) and serum IgG level <500 mg/dL (n = 32) were not associated with higher odds of prescribing PJP prophylaxis prescription (p = 0.99 and p = 0.08, respectively). There were no PJP infections in the entire cohort. Comparing patients who received PJP prophylaxis with those who were not on PJP prophylaxis, there were no significant differences in infections requiring hospitalizations, ESKD, and death (Table 3).

In a univariate logistic regression analysis, PJP prophylaxis and specifically using trimethoprim-sulfamethoxazole did not decrease infection rates requiring hospitalizations, ESKD, or death. Glucocorticoid use, however, was associated with increased rates of infections requiring hospitalizations (OR: 5.54 [95% CI: 2.01–15.4]) and death (OR: 4.67 [95% CI 1.36–15.71]) even after adjustment for age, gender, and use of PJP prophylaxis (Table 4).

Discussion

In our cohort, there were no cases of PJP pneumonia in AAV patients on maintenance rituximab therapy and very low dose of maintenance prednisone (~1 mg/day), even though 56% of patients did not receive PJP prophylaxis. Contrary to data published from a post hoc analysis of the RAVE trial, which focused on the induction phase of AAV management [11], PJP prophylaxis in our study did not decrease infection rates requiring hospitalizations. On the other hand, glucocorticoid use was associated with increased rates of infections requiring hospitalization and death, consistent with prior data [8]. PJP prophylaxis is favorable for infection prevention in the induction phase, but its role remains unclear in the maintenance phase of AAV management. This additionally highlights the need to focus on glucocorticoid-sparing agents in both the induction and maintenance phases [12–15].

Current guidelines do not specify whether prophylaxis is warranted during the maintenance phase of treatment. The 2021 American College of Rheumatology/Vasculitis Foundation (ACR/VF) guidelines for GPA and MPA "conditionally recommend prophylaxis to prevent PJP" for patients on rituximab, but note a lack of moderate or high-quality evidence to guide decision-making [16]. The 2023 Kidney Disease Improving Global Outcomes (KDIGO) guidelines specify that TMP-SMX or

Table 2. Characteristics of patients on PJP prophylaxis and not on PJP prophylaxis

	PJP prophylaxis (n = 57)	No PJP prophylaxis (n = 72)	p value
Age, years	54 (16)	56 (17)	0.71
Gender			
Male	30 (53)	48 (67)	
Female	27 (47)	24 (33)	0.15
Relapsing disease	17 (30)	28 (39)	0.38
Duration of rituximab, years	3.6 (2.5)	3.1 (2.1)	0.30
Duration of rituximab, years			
<1	7 (12)	10 (14)	
1–1.9	12 (21)	14 (20)	
2–2.9	3 (5)	11 (15)	
3–4	7 (12)	11 (15)	
>4	28 (49)	26 (36)	0.34
Prednisone dose, mg	0.66 (1.87)	1.13 (2.47)	0.23
CD4 count, cells per cubic millimeter	667.3 (328.4)	645.8 (318.9)	0.95
CD4 count, cells per cubic millimeter			
<200	2 (4.9)	3 (6.0)	1.00
>200	39 (95)	47 (94)	1.00
Serum IgG level, mg/dL	630.5 (265.9)	668.4 (276.1)	0.24
IgG level, mg/dL			
<300	3 (7.9)	5 (7.9)	
300–499	15 (31)	9 (14)	
500–699	13 (27)	24 (38)	
≥700	17 (35)	25 (40)	0.18
Organ involvement			
Kidney	46 (81)	63 (88)	0.33
Lung	45 (79)	37 (51)	<0.01
Sinus	28 (49)	37 (51)	0.86
Cardiac	0	5 (7)	0.07
Skin	7 (12)	8 (11)	1.00
Nerve	9 (16)	15 (21)	0.50
Eye	9 (16)	11 (15)	1.00
Muscle	2 (4)	0	0.19
Joint	11 (19)	16 (22)	0.83
Gastrointestinal	0	2 (3)	0.50

Numeric continuous values are presented as mean (±SD) and categorical variables as n (%).

Table 3. PJP infections, infections requiring hospitalizations, ESKD, and death in patients on PJP prophylaxis and not on PJP prophylaxis

	PJP prophylaxis (n = 57)	No PJP prophylaxis (n = 72)	p value
PJP infections	0	0	0
Infections requiring hospitalizations	8 (14)	14 (20)	0.48
ESKD	3 (5.3)	8 (11)	0.34
Death	3 (5.3)	9 (13)	0.23

PJP, *Pneumocystis jirovecii* pneumonia; ESKD, end-stage kidney disease. Data are expressed as n (%).

Table 4. Univariate logistic regression analysis of factors associated with outcomes

	Infections requiring hospitalizations		Death		End-stage kidney disease	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, years	1.03 (1–1.06)	0.08	1.03 (0.99–1.08)	0.13	1.02 (0.98–1.07)	0.28
Kidney involvement	0.55 (0.19–1.88)	0.31	–	–	–	–
PJP prophylaxis use	0.68 (0.25–1.71)	0.42	0.53 (0.14–1.72)	0.31	0.44 (0.09–1.62)	0.25
trimethoprim-sulfamethoxazole use	0.44 (0.12–1.28)	0.16	0.37 (0.06–1.15)	0.21	0.47 (0.07–1.93)	0.35
Glucocorticoid use	5.54 (2.01–15.4)	0.00	4.67 (1.36–15.71)	0.01	0.97 (0.14–4.1)	0.97
IgG level <500 mg/dL	1.86 (0.66–5.07)	0.23	0.8 (0.17–2.92)	0.76	0.92 (0.19–3.43)	0.90
CD4 count <200 cells per cubic millimeter	3.16 (0.39–20.68)	0.23	–	–	–	–
Relapsing disease	1.37 (0.52–3.47)	0.52	2.39 (0.75–7.91)	0.14	1.62 (0.44–5.72)	0.45

PJP, *Pneumocystis jirovecii* pneumonia.

alternative "is advised for pneumocystis pneumonia prophylaxis for 6 months following rituximab induction," with consideration of longer use for patients with structural lung disease, or patients with ongoing immunosuppression or glucocorticoids [17]. The 2020 Canadian Vasculitis Research Network recommends that PJP prophylaxis be given during induction and extend to "at least 6 months following the last rituximab dose" and similarly notes a paucity of evidence to inform duration [18]. The 2022 EULAR guidelines introduced a new recommendation concerning PJP prophylaxis. They stated, "for patients with AAV receiving RTX, cyclophosphamide, and/or high doses of glucocorticoids, we recommend the use of TMP-SMX as prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) and other infections" without explicitly commenting on the maintenance phase of treatment. EULAR suggests that it appears reasonable to continue this drug for the anticipated duration of the biological effect of CYC and RTX, which is approximately 3 and 6 months after the last dose or until B cell reconstitution occurs [19].

Although the overall incidence of PJP pneumonia is low, mortality is high, thus the decision to discontinue PJP prophylaxis during maintenance is potentially of great consequence [20–22]. In a trial of rituximab versus azathioprine for maintenance in AAV, PJP prophylaxis was required for all patients with CD4 counts <250 cells per cubic millimeter. There was a single case of PJP in the rituximab group [3]. In the follow-up study evaluating a tailored rituximab maintenance regimen, all patients were in remission and on PJP prophylaxis, and there were no cases of PJP [4]. On the other hand, long-term exposure to PJP prophylaxis may result in unwanted side effects, including higher risk of leukopenia (HR: 3.1; 95% CI: 1.1–8.6), rash (HR: 1.9; 95% CI: 1.0–3.6), and nephropathy (HR: 2.6; 95% CI: 1.3–5.1) [9].

Yang et al. concluded that age at the time of diagnosis, smoking, pulmonary involvement, baseline SCr ≥5.74 mg/dL, CD4 count <281 cells per cubic millimeter, and intravenous cyclophosphamide therapy were risk factors for complicated infection in patients with AAV [23]. This likely explains why lung involvement was associated with increased odds of PJP prophylaxis in our study. With regards to CD4 count, few patients in our study were found to have a CD4 count <200 cells per cubic millimeter, and this was not associated with increased prescription of PJP prophylaxis. While CD4 count guides PJP prophylaxis in the HIV population, current guidelines do not address this potential variable in AAV management. Some authors, such as Wolfe et al. argue that CD4 count should be factored into the risk-benefit discussions when considering prophylaxis duration [24]. Others advocate for prophylaxis for patients with lymphopenia, given data showing an increased risk of PJP. Winthrop et al. [25] propose a prophylaxis prescribing scheme specific to GPA and MPA that permits discontinuation when prednisone is less than 15 mg, conditional on the presence of fewer than two risk factors including lymphopenia, low CD4 count, cyclophosphamide use, rituximab use, or initial prednisone dose greater than 60 mg.

Limitations of our study include its retrospective nature, which limits the ability to draw high-quality conclusions and recommendations. The lack of data on drug adherence and drug reactions might have impacted the decision-making process regarding whether to continue or discontinue PJP prophylaxis. While the dose of

glucocorticoids in both arms was low, it was not zero, and this might have influenced decisions on PJP prophylaxis prescription. Furthermore, in some patients, CD4 and serum IgG levels were not assessed consistently. Lastly, the type of infections requiring hospitalizations and nonhospital infections were not evaluated.

In this retrospective analysis of the use of PJP prophylaxis in AAV patients on rituximab maintenance monotherapy, no episodes of PJP infections were observed, irrespective of the use of PJP prophylaxis. Given the evolving nature of recommendations and the presence of uncertainties in this area, high-quality studies are needed.

Statement of Ethics

This study is in compliance with the guidelines for human subjects and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board at Johns Hopkins University School of Medicine, Approval No. IRB00121955. Written informed consent was waived by the Institutional Review Board at Johns Hopkins University School of Medicine since this was an exempt IRB (IRB00121955).

Conflict of Interest Statement

Duvuru Geetha is a consultant to ChemoCentryx, GSK, Otsuka, Calliditas, Amgen, and Aurinia Inc. Other authors including Faten Aqeel, Michael Cammarata, and Dustin Le have no conflicts of interest to declare.

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Author Contributions

Conception of research question: D.G. and F.A.; study design and conduct: D.G.; statistical analyses: D.L.; interpretation of results: all authors (D.G., F.A., D.L., and M.C.). All authors reviewed, revised, and approved the manuscript for submission.

Data Availability Statement

The data underlying this article are available in the article. Further inquiries can be directed to the corresponding author, Faten Aqeel.

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