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Original Article

Rituximab versus azathioprine in maintenance therapy of patients with granulomatosis with polyangiitis

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Abstract

Background: Granulomatosis with polyangiitis (GPA) is a rare disease affecting medium-small vessels, causing granuloma formation and inflammation. This study aimed to assess the efficacy and safety of RTX versus Azathioprine (AZA) for maintenance treatment in GPA patients.

Methods: This retrospective cohort study involved a review of medical records of recently diagnosed GPA patients undergoing maintenance treatment with RTX or AZA. The main variable was the frequency of relapses within an 18-month follow-up period. Additionally, the study compared changes in BVAS.WG score (The Birmingham Vasculitis Activity Score-Wegner specific) and Damage (vasculitis damage index (VDI)), mortality, and treatment complications between the two groups.

Results: Among the 43 patients receiving RTX maintenance treatment, 8 (18.6%) experienced relapses during 24 months follow-up, while 14 (66.6%) out of the 21 patients receiving AZA relapsed (Hazard Ratio = 6.9 and 95% confidence interval = 1.95-19.3, p <001). Notably, the increase in the BVAS-WG score was significantly lower in the RTX group compared to the AZA group (p <001). The cumulative steroid dose was 143±21 mg in the RTX group and 125±25 mg in the AZA group (P = 0.1). Treatment side effects were similar in both groups (p >0.05).

Conclusion: Maintenance treatment with RTX is associated with better treatment response and lower relapse rate compared to AZA. There was no difference in treatment complications between AZA or RTX in maintenance treatment.

Keywords: Granulomatosis with polyangiitis (GPA), Rituximab, Azathioprine, Antineutrophilic Cytoplasmic Antibody (ANCA).

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Granulomatosis with polyangiitis (GPA), previously known as Wegner's granulomatosis, is a necrotizing vasculitis that affects medium-small vessels and causes granuloma formation and inflammation. Anti-neutrophil cytoplasmic antibodies (ANCA) are known antibodies that play a role in the pathogenesis of the disease. The upper and lower respiratory tract and kidneys are primarily involved in this disease. GPA can be limited to the respiratory tract or an extended disease affecting multiple organs (1, 2). GPA is a rare disease with a prevalence of 3.0 per 100,000 persons in the USA (3).The diagnosis of GPA is based on clinical presentations, histological findings, and autoantibodies (4). The management of the GPA involves an induction phase to decrease inflammation and achieve remission. Following this, maintenance therapy options such as azathioprine (AZA), rituximab (RTX), and mycophenolate mofetil combined with low-dose glucocorticoids (GCs) are used for sustained remission (5, 6). Rituximab is an anti-CD20 monoclonal antibody increasingly used to treat ANCA-associated vasculitis (AAV), leading to B-cell depletion lasting 6-12 months (7, 8).

The duration of maintenance treatment with RTX is 18 months, but the optimal duration is still under question (9). Longer maintenance durations were related to lower relapse rates in studies for both RTX and AZA (10, 11). A wide range of complications, such as infection, psoriasis, and lowered vaccination outcomes, are reported with RTX treatment (12). Given the low prevalence of Wegner's disease, the conduct of a cohort study to evaluate the optimal treatment options for induction and maintenance therapy for patients with GPA is uncommon. The study specifically aimed to compare the effectiveness and safety of RTX and AZA for maintenance treatment.

Methods

Study design and patients: This retrospective cohort study involved a review of documents from GPA patients diagnosed between 2017 and 2021 at Amiralam Hospital, Tehran, Iran. Diagnosis of the disease was based on Chapel Hill ACR1994 and the European Medicine Agency (EMA) algorithm (13). We included documents of all patients who received maintenance treatment with RTX or AZA after complete remission with induction therapy (cyclophosphamide or RTX).

The Birmingham Vasculitis Activity Score-Wegner specific (BVAS.WG) is used to define disease activity (14). The remission was determined based on BVAS WG=0. Patients were categorized into cyclophosphamide (CYC)-AZA and RTX-RTX groups based on their induction and maintenance treatment.

Inclusion criteria: All patients with recently diagnosed GPA who have received treatment with RTX-RTX (induction-remission) or CYC-AZA at the Rheumatology clinic of Amiralam Hospital, with a minimum 24-month follow-up.

Exclusion criteria: 1. Patients with incomplete medical records 2. Patients with a history of relapse 3. Patients with prior treatment with RTX or CYC 4. Patients outside the age range 20-80 5. Patients receiving treatment with other Disease-Modifying Antirheumatic Drugs (DMARDs).

Data collection: Our comprehensive data collection process involved extracting a wide range of patient information from their clinical records, including demographic details, clinical presentation, year of disease diagnosis, signs and symptoms in the first presentation, follow-up duration, clinical outcomes including organ involvements, and severity of organ involvements based on BVAS-WG scoring. Medication history in the induction and maintenance phase and laboratory data (ESR, CRP, LFT, Cr, U/A, CBC, MPO ANCA, PR3 ANCA) were also collected from each patient's document.

Treatment protocol: Patients were categorized into two groups based on their treatment protocol. The first group was treated with RTX for induction and remission. The induction treatment involved administering RTX at a 2-gr dose for induction (500mg weekly for 4 weeks) and methylprednisolone 1 gr for three days. This was followed by a maintenance dose of RTX 1 gram every six months, along with 1mg/kg/daily prednisolone. The second group was administered AZA and prednisolone for maintenance after CYC induction therapy (CYC 1 gr monthly for six months). Additionally, they received 1 gr methylprednisolone for three days during induction treatment. The prescription for AZA was as follows: AZA 2.5 mg/kg/daily for six months, then continued with a dose of 2mg/kg/daily for six months and 1.5mg/kg/daily for another six months. All patients had a routine visit and lab tests every two months, with a gradual tapering of prednisolone dosage to reach a daily dose of 5mg over six months.

Outcome and characteristics: The primary variable in this study was the percentage of relapse during the 18-months follow-up period. Major relapse was characterized by a BVAS.WG increase exceeding three points, while minor relapse involved an increase of three or fewer points. BVAS.WG scores were diligently tracked every two months during follow-up visits and in patients exhibiting signs of disease progression. The vasculitis damage index (VDI) is a clinical tool for evaluating the degree of damage in systemic vasculitis (15). We calculated the changes in the VDI score 24 months after the beginning of the maintenance regime.

Statistical analysis: We collected all data from the hospital and clinic records of all patients diagnosed with a GPA who met the inclusion criteria between 2017 and 2021. SPSS Version 25 was used for statistical analysis. To show demographic characteristics and clinical symptoms, indicators such as mean and standard deviation (for continuous variables) and also frequency and percentage of data (for ordinal variables) were used. Median and quartile deviation were used to describe continuous variables with non-normal distribution. Pearson's chi-square test - or Fisher's exact test in case of violation of assumptions - was used to compare pairwise results. In addition, results were compared between two groups using independent Student's t-test (in case of normal distribution) and Wilcoxon test (in case of non-normal distribution). All statistical tests were two-sided, and p-values less than 0.05 were considered significant.

Results

64 individuals. Among them, 43 received RTX-RTX treatment, while 21 were treated with CYC-AZA. The mean± SD age in the RTX group was 40.9±16.0, and in the AZA group was 42.1±16.4 (P=0.7*)*. The male proportion was 58% (n=25) in the RTX group and 67% (n=14) in the AZA group, with no significant difference (P=0.5). Of 64 patients, 14 had an ANCA negative test, 43 had PR3 ANCA, and 7 had an MPO ANCA positive test. There were no statistically significant differences in ANCA results between the two groups. The most common clinical symptoms were related to the ear, nose, and throat. Other organs like the lung, kidney, eye, and nervous system were involved at the time of diagnosis. All of these presentations had the same distribution among the two groups (table 1).

After achieving remission, 22 patients experienced at least one relapse within an 18-months follow-up period. Eight (18.6%) patients were from the RTX group, and 14 (66.6%) were from the AZA group (HR 6.9 95% CI 1.95-19.3; P=0.001) (table 2). Major relapse did not happen in the RTX group, but 21.4% of all the relapses in the AZA group were major (p<0.001). 18.6% of the RTX group and 38.1% of patients in the AZA group experienced a relapse in the first six months of beginning the maintenance treatment; this difference wasn't statistically significant(P=0.09) (table 3). The BVAS score was zero in all patients on the first maintenance visit. The mean of standard deviation for the BVAS score in 18 months follow-up was 0.15±0.04 in the RTX group and 0.5±1.6 in the AZA group (p<0.001). There was no mortality in each group in 24 months follow-up. The mean of VDI at the beginning of maintenance was similar between the two groups (table 1). At month 18, the Mean of VDI in the RTX group reached 1.3±1.0 and the AZA group to 1.7±0.9 (P=0.1). In an 18-month follow-up, there was no statistically significance difference (P=0.1, t=1.4) between cumulative corticosteroid dose in RTX (143± 21) and AZA (125±25) groups. Through meticulous analysis of individuals who relapsed post maintenance, we aimed to identify potent markers for predicting relapse using both univariable and multivariable approaches. First, we identified the variables that had p>0.2 in the univariable analysis and entered them in multivariable analysis (PR3-positivity, pulmonary, mucous-eye involvement, and treatment group). As shown in table 4, the maintenance treatment group (AZA or RTX) was the only variable related to increased relapse risk (HR 9.2 95% CI 2.3-36). There was no difference between the two groups in treatment complications (table 5).

Table 1. Comparison of demographics, clinical presentations, and lab data at patients' first maintenance visit

Variables	Rituximab N=43	Azathioprine N=21	*P*-value
Age, Mean±SD	40.9±16.0	42.1±16.4	0.7
Male/Female, n	18/25	7/14	0.5
ANCA negative	10 (23.3%)	4 (19%)	0.7
PR3+	29 (67.4%)	14 (66.7%)	0.9
MPO+	4 (9.3%)	3 (14.3%)	0.5
Cr>1.3	6 (14%)	3 (14.3%)	0.9
General manifestations at remission	11 (25.6%)	8 (38.1%)	0.3
Cutaneous manifestations in remission	7 (16.3%)	4 (19%)	0.7
Mucous/eye manifestations	17 (39.5%)	7 (33.3%)	0.6
ENT manifestations	43 (100%)	21 (100%)	-
Pulmonary manifestations	32 (74.4%)	16 (76.2%)	0.8
Alveolar hemorrhage	2 (4.3%)	0	0.4
Renal manifestations	29 (67.4%)	11 (52.4%)	0.2

Variables	Rituximab N=43	Azathioprine N=21	*P*-value
Nervous manifestations	8 (18.6%)	5 (23.8%)	0.6
Cumulative prednisolone until remission	95±17	88±31	0.5
VDI at maintenance	1.2±1.0	1.6±0.9	0.1
Hx of previous cardiac disease	0	0	1
Hx of diabetes mellitus	3 (6.9%)	2 (9.5%)	0.6
Hx of Hypertension	5 (11.6%)	3 (14.2%)	0.7
HX of renal disease	22 (51.1%)	10 (47.6%)	0.6
Mortality during 24-months follow-up	0	0	

SD: standard deviation. ANCA: Anti-neutrophil cytoplasmic antibody. Cr: Creatinine. GPA: Granulomatosis with polyangiitis. PR3: Proteinase 3 antibody. MPO: Myeloperoxidase .VDI: Vasculitis Damage Index. Hx: history.

Table 2. Relapse during 18-month follow-up after maintenance

Relapse during 18-month follow-up after maintenance.			Relapsed after maintenance		Total
			No	Yes	
Maintenance. Gp	**RTX.RTX**	Count	35	8	43
		% within Maintenance. GP	81.4%	18.6%	100.0%
	CYC.AZA	Count	7	14	21
		% within Maintenance. GP	33.4%	66.6%	100.0%
Total		Count	42	22	64
		% within Maintenance. GP	65.6%	34.4%	100.0%

Gp: group. RTX: Rituximab. CYC: Cyclophosphamide. AZA: azathioprine.

Table 3. Remained relapse-free at least six months after maintenance therapy

Remained relapse-free at least six months after maintenance therapy			Relapsed in 6 months?		Total
			No	Yes	
Maintenance. GP	**RTX.RTX**	Count	35	8	43
		% within Maintenance. GP	81.4%	18.6%	100.0%
	CYC.AZA	Count	13	8	21
		% within Maintenance. GP	61.9%	38.1%	100.0%
Total		Count	48	16	64
		% within Maintenance. GP	75.0%	25.0%	100.0%

Gp: group. RTX: Rituximab. CYC: Cyclophosphamide. AZA: Azathioprine.

Table 4. Uni and multivariable analysis for relapse

Variable	HR (95% CI)	P-value
Univariate analysis		
Age (years)	1 (0.97-1.03)	0.8
PR3 vs MPO or ANCA negative	2 (0.6-6.2)	0.19
Cr>1.3	0.5 (0.09-2.6)	0.4
Renal Involvement	0.9 (0.31-2.7)	0.7
Pulmonary Involvement	5 (1.02-24.4)	0.047
Nervous Involvement	0.5 (0.1-2.0)	0.3
Mucous-eye involvement	3 (1.02-8.1)	0.045
Maintenance group (Azathioprine vs Rituximab)	6.91 (1.95-19.3)	0.002
Multivariate Analysis		
PR3 vs MPO or ANCA negative	1.09 (0.2-5.1)	0.9
Pulmonary Involvement	4.3 (0.7-25)	0.1
Mucous-eye involvement	2.3 (0.7-14)	0.1
Maintenance group (Azathioprine vs Rituximab)	9.2 (2.3-36)	0.01

HR: Hazard Ratio.

Table 5. Treatment complications in AZA and RTX group

Treatment complication	AZA group N (%)	RTX group N (%)	P-value
Infection	0	4 (9%)	0.2
Cytopenia	3 (14%)	1 (2%)	0.09
LFT rising	1 (4%)	1 (2%)	0.7
Haire loss	1 (4%)	0	0.3
erosive gastritis	0	1 (2%)	1

AZA: Azathioprine. RTX: Rituximab. LFT: Liver function test.

Discussion

In this retrospective cohort study, data from GPA patients receiving maintenance treatment with AZA or RTX for Wegner's disease were analyzed to compare the safety and effectiveness of the two treatments. The Canadian Vasculitis Research Network recommended RTX as a first-line in remission induction and maintenance therapy (16). The study by Specks et al. shows a single course of rituximab (a total four-week, 375 mg per square meter of body surface area administrated each week) had the same effect as 18 months of immunosuppressive therapy (CYC for induction and AZA for remission) in patients with severe AAV.(17) The MAINRISRAN trial by L. Guillevin et al. revealed that AAV patients receiving RTX for maintenance treatment achieved more sustained remission (in 28-month follow-up) than those receiving AZA. Major relapse occurred in 5% of the RTX group and 28% in the AZA group, with similar incidence of severe adverse effects in both groups (18). B. Terrier et al. conducted a separate study, publishing a prospective 60-month follow-up of the patients in the MAINRITSAN trial, which indicated a lower relapse risk in the RTX-treated group (19) In our study, patients receiving RTX in maintenance exhibited a higher treatment response and lower relapse rates (major and minor) compared to the AZA group. It is noteworthy that no major relapses occurred in the RTX group, consistent with findings from other studies on RTX maintenance treatment among AAV patients. Importantly, our study specifically

focused on GPA patients. According to the EULAR 2022 recommendations for AAV management, RTX is recommended for remission therapy, with AZA and MTX as alternative treatments. Additionally, longer maintenance treatment (24-48 months) for new onset AAV is considered superior to shorter durations (20). In our study, both the AZA and RTX groups had an 18-months maintenance treatment period. Further studies are needed to evaluate the impact of maintenance treatment duration on relapse risk. In our analysis, we considered variables such as age, remission treatment group, and the presence of renal, eye, or pulmonary involvements, as well as ANCA (PR3 OR MPO) to assess relapse risk. Our findings indicated that the remission treatment group was the only factor linked to relapse risk. B. Terrier et al. found that PR3-ANCA positive AAV patients had a higher risk of relapse over follow-up (19). In the long-term follow-up of maintenance treatment with RTX in AAV patients, PR3-ANCA positivity was related to relapse risk (21).

Our study found that GPA patients with PR3 positivity experienced more relapses during the 24-month follow-up, although this was not statistically significant. To draw a more accurate conclusion about the association between PR3-ANCA and relapse in GPA patients, longer follow-up periods or studies with larger populations are necessary. A higher dose of prednisolone is related to a higher risk of infection (22). In our study, the prednisolone dose was gradually reduced over six months. In recent studies, Stepwise reduction in the dose of prednisolone and reaching 5mg/daily over 4-5 months is recommended (23). This protocol, based on the PEXIVAS trial, emphasizes a 50% reduction in prednisolone in the second week of starting GCs, leading to a lower cumulative dose and reduces side effects (24). According to the study by Besada et al., 57% of GPA patients experienced hypogammaglobulinemia during treatment with RTX, and 26% of patients had a severe infections (25). These side effects were also reported in the same studies (26, 27).

In our research, we observed no statistically significance difference in the incidence of Treatment complications, such as infection, cytopenia, hair loss, and erosive gastritis between the two treatment groups (AZA and RTX). In GPA patients, maintenance treatment with RTX demonstrates a superior treatment response and lower relapse rate compared to AZA. Notably, there was no difference in treatment complications between AZA or RTX. Therefore, Rituximab emerges as an effective option for maintenance therapy among GPA patients. The research was conducted at AmirAlam Hospital, a specialized Ear, Nose, and Throat center in Tehran, Iran. The prevalence of ENT manifestations among patients due to the hospital specialty was a notable limitation as it was a single-center study. Subsequent large multi-center studies hold promise for enhancing research quality.

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Ethics approval: This project was approved by the Research Ethics Committees of the School of Medicine – Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1398.448).

Conflict of interests: There is no conflict of interest to declare.

Authors' contribution: FF and DA designed the conception of the study; FMH, BM and FF focus of the statically analysis; DA and FMH technical support and conceptual advice. All authors contributed to the draft of the manuscript, revised it critically, and approved the final version.

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