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Original Article

Rituximab-associated hypogammaglobulinemia in ANCA-associated vasculitis: Incidence and time course

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Abstract

Objective: Rituximab (RTX) is approved for remission induction and maintenance of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV). Observational studies demonstrate decline in immunoglobulin (IgG) in AAV post-RTX. The time course for the onset of hypogammaglobulinemia (Hypo-IgG) post-RTX is unknown. This is a key determinant in deciding whether to continue RTX for reinduction or maintenance of remission for AAV. We evaluated the trends of Hypo-IgG among AAV patients post-RTX therapies.

Methods: An observational single-tertiary-center study of AAV patients treated with RTX for remission induction or maintenance (induction therapy, maintenance therapy, and combined induction and maintenance therapy) between 1998 and 2018. Poisson regression was used to compare the incidences of Hypo-IgG: mild (450-700 mg dL^{-1}), moderate (200-450 mg dL^{-1}), and severe ($\leq$200 mg dL^{-1}). Ig levels were measured every 3-6 months after RTX use.

Results: Mean (SD) age at last visit was 59 (16) years, 93% were Caucasians, 64% were females, and 71 (63%) had granulomatosis with polyangiitis (GPA). Hypo-IgG occurred in 47 patients: one (2%) severe, 13 (28%) moderate, and 33 (70%) mild. Lower incidences of mild Hypo-IgG post-RTX were seen during induction compared to maintenance (IR 5.04 per 100 000 days vs 5.45 per 100 000 days, incidence rate ratio (IRR) 1.08, 95% CI 0.34, 3.19). Moderate Hypo-IgG occurred at 2.29 per 100 000 days during induction and 1.82 per 100 000 days during maintenance (IRR 0.79, 95% CI 0.08, 4.84).

Conclusion: Hypo-IgG is common among AAV treated with RTX, occurring in 42% of patients in this single-center cohort. The nadir IgG levels occur during remission induction, and the IgG levels remain relatively stable or increase over time in those receiving RTX for remission maintenance.

Keywords: ANCA, vasculitis, rituximab, hypogammaglobulinemia, IgG

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Introduction

ANCA-associated vasculitis (AAV) is a systemic necrotizing small vessel vasculitis characterized by the presence of circulating antineutrophil cytoplasmic antibodies (ANCA). The canonical forms of AAV include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA); all of these diseases are characterized by relapsing disease courses, which are associated with substantial morbidity and mortality. Early diagnosis and treatment are essential for controlling disease progression and renal survival. High doses of cyclophosphamide and glucocorticoids were gold standard for the treatment of the AAV; however, their acute and long-term side effects were substantial.[1] Thus, rituximab (RTX) (Genentech; San Francisco, United States), which is approved for remission induction and maintenance in AAV, is now commonly used.[2–6]

RTX depletes B cells that express CD20 but does not directly affect B cell precursors or antibody-producing plasma cells. Thus, theoretically, patients receiving RTX should still have production of protective antibodies from previously encountered agents, and there should be replenishment of the peripheral B cells by B cell precursors following RTX therapy. This renders RTX a relatively safe treatment option. However, some evidence suggests that RTX depletes preplasma B cells and may decrease production of antibody-producing plasma cells, particularly to nascent antigens.[7,8] This may lead to hypogammaglobulinemia (Hypo-IgG), which may predispose patients to serious infections.[7,9]

Several observational studies have demonstrated a decline in serum IgG in AAV patients treated with RTX.[7,10–12] The RTX-associated Hypo-IgG is mostly transient, but in some patients - particularly in those who received multiple courses of RTX - the Hypo-IgG could be more severe and persistent.[9,13] The Hypo-IgG becomes important in clinical decision-making as it may preclude further use of RTX in patients who

would benefit from further course of RTX. We evaluated the trend of Hypo-IgG among RTX-treated AAV patients. We sought to describe the incidences of Hypo-IgG in these patients and to identify factors associated with more severe forms of Hypo-IgG.

Methods

Patients with a diagnosis of AAV seen in the clinics of the Johns Hopkins University, Division of Rheumatology, between 1998 and 2018 were included. Patients were classified as having GPA, MPA, or EGPA using the 2012 Chapel Hill Consensus criterion.[14] Inclusion criteria for the study were the use of RTX for remission induction and/or remission maintenance, grouped as the following: induction, maintenance, and combination (both induction and maintenance). Maintenance group was comprised of patients on other immunosuppression (i.e., cyclophosphamide or methotrexate). We further restricted the study cohort to patients who had follow-up visits during the study period, defined as "visits." Visit 1 was defined as the first visit and measurement of laboratory indices following the first exposure to RTX. RTX was administered to the patients seen at least every 4-6 months, and most were seen 3-4 times a year. This study was approved by the Ethics Committee of the Johns Hopkins Institutional Review Board. This study was performed in accordance with best research practices and institutional guidelines, in addition to the accordance with the World Medical Association's Declaration of Helsinki.

Main Points

- Early diagnosis and treatment are essential for controlling ANCA-associated vasculitis disease progression and renal survival, but conventional therapies including high doses of cyclophosphamide and glucocorticoids cause acute and long-term side effects; thus, rituximab is approved for remission induction and maintenance in ANCA-associated vasculitis.
- Despite its widespread use and the risk of developing hypogammaglobulinemia from rituximab, there have been different guidelines established for clinical monitoring of hypogammaglobulinemia, which may preclude further use of rituximab in patients who would benefit from further course of rituximab.
- Among 113 rituximab-treated patients with ANCA-associated vasculitis (i.e., induction (n = 30), maintenance (n = 14), and combination (n = 69)) at a large, single-tertiary referral center, we observed 26% (n = 29) of the rituximab-treated patients who developed a decline in serum IgG to concentrations below 700 mg dL^{-1} and in 10% (n = 11) who developed concentrations below 500 mg dL^{-1}.
- Our study demonstrates that of those who developed moderate or severe hypogammaglobulinemia, the nadir IgM was observed after clinical visit 2 or 3, similar to the trend in the nadir of IgG post-rituximab therapy. Comparison of the first Ig measurement after rituximab, repeat Ig measurements from follow-up were not statistically significant.

Demographics, clinical data, and RTX therapy were extracted. We considered "remission induction" as RTX dosed at 375 mg m^{-2} once a week for 4 weeks or 1 g RTX every 2 weeks for two doses along with prednisone 1 mg kg^{-1} day^{-1} tapered to ≤5 mg by month 6 (Table S1). "Remission maintenance" therapy was defined as RTX dosed at 500 mg or 1,000 mg every 4-6 months (Table S1). Clinical laboratory measurements included Ig levels (i.e., IgG, IgA, and IgM), measured every 3-6 months after RTX use, white blood cells, hemoglobin, platelets, serum creatinine, estimated glomerular filtration rate (eGFR), aspartate aminotransferase, alanine aminotransferase, and proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA. Since most patients did not have their baseline IgG levels checked, we considered the first IgG level at "Visit 1" post-initial RTX administration.

Severity of Hypo-IgG was defined as mild (450-700 mg dL^{-1}), moderate (200-450 mg dL^{-1}), and severe (≤200 mg dL^{-1}), similar to the reference ranges in a recent study.[15] eGFR was calculated using the Modification of Diet in Renal Disease equation[16] at the time of enrollment. Infections over the course of follow-up were recorded as severe adverse effects.

Statistical analysis

Binary outcomes were compared between treatment arms using Chi-square or Fisher's exact test. Continuous outcomes were compared by Wilcoxon's rank sum test. Descriptive data are presented as mean with standard deviation (SD) and/or median with interquartile range (IQR). We assessed the associations between the nadir IgG concentration and potential risk factors using Poisson regression to calculate the incidence rate ratio (IRR) of hypo-IgG comparing the induction vs maintenance groups, and combination vs induction only. Univariate analyses conducted for sex, race, age at last visit, use of previous immunosuppression, and ANCA status. Multivariate analyses adjusted for race when comparing the IRR of Hypo-IgG in any of the RTX therapies, maintenance vs induction and combination vs induction only. The multivariate models were created through stepwise elimination of variables of interest from univariate analysis while biologically relevant variables were retained, with the intent of using one variable for every 10 outcomes to avoid overfitting of the model. A *P*-value <.05 was considered statistically significant. We also explored the trends of IgG, IgM, IgA, and CD20 counts over time. All analyses were done using STATA 15.1 (STATA Corp, College Station, USA).[17]

Results

A total of 113 RTX-treated patients with AAV were identified (i.e., induction (n = 30), maintenance (n = 14), and combination (n = 69)), and their characteristics are summarized in Table 1. The mean (SD) age at the last visit of follow-up was 59 (16) years, 93% were Caucasians, and more than half (64%) were females. The duration of follow-up was mean 1313 (1286) days and median 953 (1256) days.

The majority (63%) of patients were diagnosed with GPA (n = 71), 33% had MPA (n = 37), and only 4% had EGPA (n = 5). The majority of patients were PR3-ANCA positive (n = 66), 44 patients were MPO-ANCA positive, and two patients were ANCA negative. Among the different ANCA types, PR3 was positive in 61 (93%) GPA, four (6%) MPA, and one (2%) in EGPA. A single patient was positive for both PR3 ANCA and MPO ANCA. An initial mean eGFR was 46.8 (21.6) mL min^{-1} 1.73^{-2}. Measurements from visit 1, after first RTX therapy, demonstrated mean and median (IQR) IgG levels of 701.5 (318.4) mg dL^{-1} and 615.5 (300) mg dL^{-1}, respectively. One-third (n = 34) had exposure to cyclophosphamide prior to RTX therapy.

Table 2 shows the distribution of patients and Hypo-IgG levels after initial therapy at visit 1. Cumulative incidence of Hypo-IgG occurred in a total of 47 patients, of which 12 patients were in the induction therapy, four patients were in the maintenance therapy, and 31 patients were in both induction and maintenance therapies. Majority of patients (n = 33) had mild Hypo-IgG at the first measurement of immunoglobulin levels. Severe Hypo-IgG occurred in only one patient in the induction group.

Of the 55 patients with repeat IgG during follow-up, the nadir IgM was 236 mg dL^{-1} in 18% (n = 10) of patients post-RTX therapy. Of those who developed moderate or severe

Table 1. Demographics of patients at the time of enrollment between 1998 and 2018.

Demographics	Overall
N	113
Age at last visit (year)	59.3 [15.9]
Female, n (%)	64 [56.6]
Weight (lb)	190.0 [49.8]
Height (ft)	5.1 [0.4]
Race, n (%)	
Caucasian	93 (82.3)
African-American	14 (12.4)
Asian	4 (3.5)
Other, American-Indian	2 (1.8)
Diagnosis, n (%)	
Granulomatosis with polyangiitis, GPA	71 [62.8]
Microscopic polyangiitis, MPA	37 [32.7]
Eosinophilic granulomatosis with polyangiitis, EGPA	5 [4.4]
Positive c-ANCA titer (>1:40), n (%)	13 [12]
Positive p-ANCA titer (>1:40), n (%)	28 [25]
Negative ANCA titer, n (%)	2 [1.8]
Positive MPO titer	44 (38.9)
Positive PR3 titer	66 (58.4)
Positive MPO and PR3 titer	1 (0.9)
Hematological indices	
IgG (mg dL^{-1})	701.5 [318.4]
Median [iqr]	615.5 [300]
CD20 (%)	2.8 [10.4]
White blood cell (K cu mm^{-1})	8.1 [3.1]
Hemoglobin (g dL^{-1})	12.5 [2.4]
Platelet (K cu mm^{-1})	264.9 [73.6]
Albumin (g dL^{-1})	4.3 [0.4]
C-reactive protein (mg L^{-1})	3.5 [12.1]
Erythrocyte sed rate (mm h^{-1}) Median [iqr]	18.6 [22.0]
Median [iqr]	13 [21]
Aspartate amino transferase (U L^{-1})	20.8 [12.1]
Alanine amino transferase (U L^{-1})	22.2 [16.6]
Creatinine (mg dL^{-1})	1.8 [1.5]
Glomerular filtration rate (mL min^{-1} 1.73 sqm)*	46.8 [21.6]
Hypogammaglobulinemia at visit 1, n (%)	N = 47
Mild: IgG level 450-700 mg dL^{-1}	33 [70.2]
Moderate: IgG level 200-450 mg dL^{-1}	13 [27.7]
Severe: IgG level ≤200 mg dL^{-1}	1 [2.1]
Missing IgG	31 (27.4)

Variables presented as mean (SD), unless otherwise indicated.
IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M.
*Estimated using the Modification of Diet in Renal Disease (MDRD) equation.

Hypo-IgG, the nadir IgM was observed after clinical visit 2 or 3, similar to the trend in the nadir of IgG post-RTX therapy. Comparison of baseline Ig with repeat Ig measurements from follow-up was not statistically significant ($P > .05$).

Overall, 131 incident infections occurred during the study, as demonstrated in Table 3. Between visit 1 and visit 2, 79 cases of infection occurred: one (1%) case of severe Hypo-IgG, 12 (15%) cases of moderate Hypo-IgG, and 24 (30%) cases of mild Hypo-IgG. Majority of patients had head/neck and pulmonary-related infections (i.e., pneumonia, bronchitis, upper respiratory infections, sinusitis, and otitis) between visit 1 and visit 2, and the overall trend seemed to be that these types of infections were higher compared to other infections affecting other organs.

For the overall cohort, IgG trend remained stable over time (Figure 1). We stratified the study population by follow-up of clinical visit and by type of RTX therapy. Figure 2 displays the trend of IgG over time by visits and the type of RTX therapy administered. Those with RTX-induction therapy had slightly lower incidences of mild Hypo-IgG compared to those with RTX-maintenance therapy (IR 5.04 per 100 000 days vs 5.45 per 100 000 days, IRR 1.08, 95% CI 0.34, 3.19). Moderate Hypo-IgG occurred 2.29 per 100 000 days among those with induction therapy and 1.82 per 100 000 days among those with maintenance therapy (IRR 0.79, 95% CI 0.08, 4.84). Incidence of Hypo-IgG was 1.6-fold significantly higher post-RTX dosing and remained higher after adjustment for previous immunosuppression usage, age at last visit follow-up, sex, race, and ANCA status (PR3, MPO, both) (IRR 1.60, 95% CI 1.24, 2.07; aIRR 1.53, 95% CI 1.17, 2.00; Table 4). Comparing patients with RTX for only induction, those with the combination of RTX (induction and maintenance) therapies were at significantly higher risk of Hypo-IgG (IRR 2.31, 95% CI 1.38, 3.86; aIRR 1.86, 95% CI

Table 2. Incidence of hypogammaglobulinemia (Hypo-IgG) after initial Rituximab induction, maintenance, or both by visit 1.

	Cumulative	Induction Therapy	Maintenance Therapy	Both Induction and Maintenance
IgG*				
No. patients	113	30	14	69
Missing	31	12	8	11
Hypo-IgG events	47	12	4	31
Mild Hypo-IgG	33	8	3	22
Moderate Hypo-IgG	13	3	1	9
Severe Hypo-IgG	1	1	0	0

IgG, immunoglobulin G; Hypo-IgG, hypogammaglobulinemia.
Severity of Hypo-IgG was defined as mild (450-700 mg dL^{-1}), moderate (200-450 mg dL^{-1}), and severe (<200 mg dL^{-1}).
*Number of serum IgG measurements take for each participant in the registry from visit 1 to follow-up visits. These measurements were stratified by the type of rituximab therapies (induction, maintenance, and both induction and maintenance).

Table 3. Incidence of infection and hypogammaglobulinemia (Hypo-IgG), stratified by affected organ system.

			Affected Organ System					
Visit	No. of Patients, N = 113	Incident Events, n = 131	Gastro-intestinal,† n = 8	Pulmonary,‡ n = 92	Head and Neck,§ n = 95	Genitourinary,** n = 25	Bacteremia,†† n = 20	Skin,‡‡ n = 23
1§§	113	79	1	25	33	7	4	9
Hypogammaglobulinemia								
Severe		1 (1%)						
Moderate		12 (15%)						
Mild		24 (30%)						
2	79	26	2	10	7	1	2	4
Hypogammaglobulinemia								
Moderate		6 (23%)						
Mild		7 (27%)						
3	52	15	1	4	3	4	2	1
Hypogammaglobulinemia								
Moderate		2 (13%)						
Mild		4 (27%)						
4	27	8	0	3	3	0	1	1
Hypogammaglobulinemia								
Moderate		1 (13%)						
Mild		5 (63%)						
5	14	3	0	1	1	0	0	1
Hypogammaglobulinemia								
Mild		1 (33%)						

*Affected organ system as documented by the International Classification of Diseases 9/10 for "Diagnoses" by the date of follow up "Visit," thus infections occurred anytime in between the visits.
†Diverticulitis.
‡Pneumonia, bronchitis, upper respiratory infection, influenza, mycobacterium avium intracellulare, or tuberculosis.
§Urinary tract infection.
**Sinusitis, otitis, candida esophagitis, uveitis, pharyngitis (viral or streptococcal), and mastoiditis.
††Cellulitis, herpes zoster, and measles.
‡‡Methicillin-resistant staphylococcus aureus, meningitis, joint infection, neutropenic fever, and sepsis.
§§Visit 1 includes infections that occurred post-first RTX therapy and before visit 2.

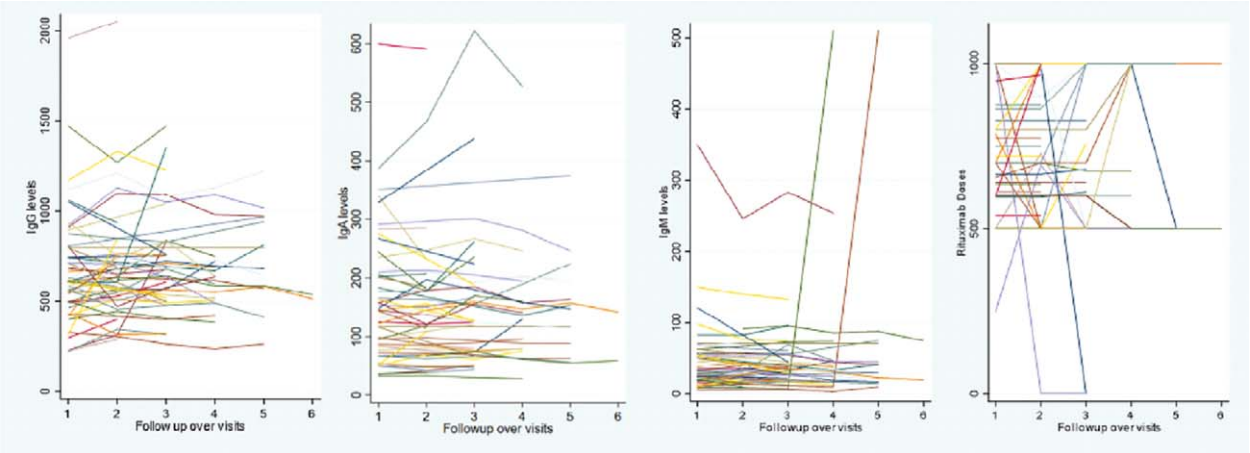

Figure 1. Trends of immunoglobulins (IgG, IgA, and IgM) and the rituximab dosages over the follow-up visits among the participants (represented by colored lines) in this cohort study.

1.10, 3.16; Table 4). The evolution of IgG remained within a narrow range, primarily for those with maintenance RTX therapy, followed by those who received RTX induction therapy. Race and previous use of immunosuppression (i.e., cyclophosphamide, methotrexate, leflunomide, and azathioprine) were independent predictors of Hypo-IgG (Table 4).

Discussion

RTX is approved for both for induction and maintenance of remission, and its use has been adopted widely within the vasculitis community. Hypo-IgG of variable severity is seen as a consequence of RTX. The time course for the development of Hypo-IgG following RTX exposure has not been well defined. This is a key factor in deciding whether to continue to use RTX for any given patient. Despite its widespread use and the

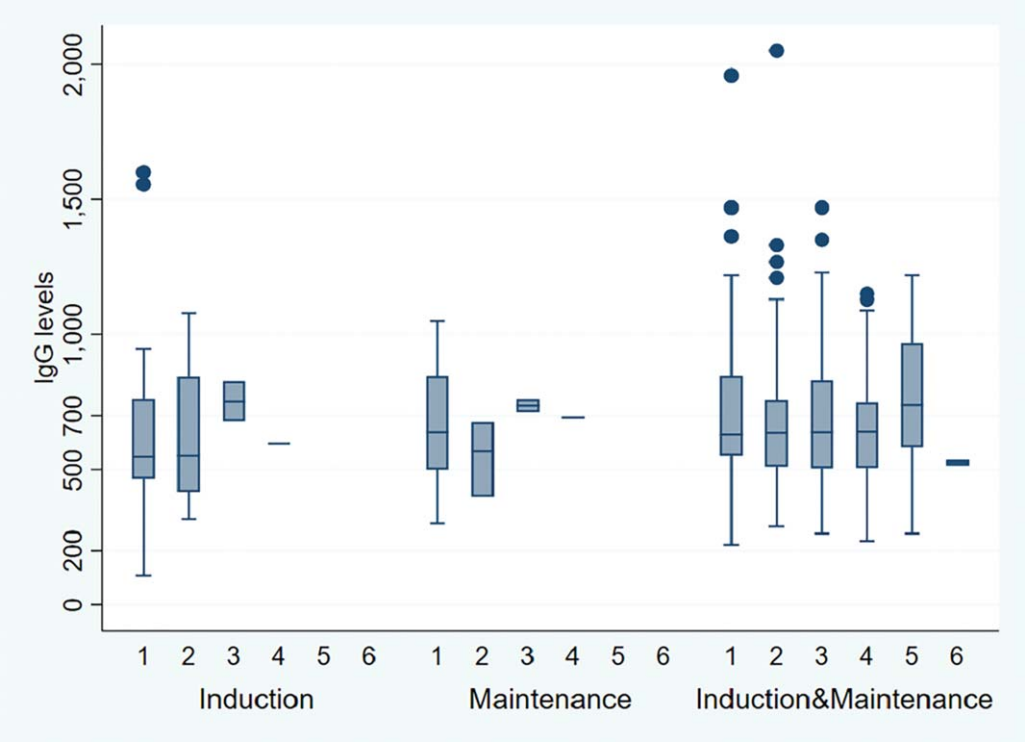

Figure 2. A box plot figure demonstrating the trends of IgG concentrations (mg dL^{-1}) by the three groups of rituximab-therapies over the follow-up visits among the participants in this cohort study. Each box plot per visit displays the range, median, and outliers (circles) of IgG levels.

Table 4. Incidence of hypogammaglobulinemia (Hypo-IgG) among Rituximab-treated ANCA vasculitis.

	IRR	95% CI		P-value	aIRR	95% CI		*P*-value
Any rituximab dosing (i.e., induction, maintenance, and combination)	1.60	1.23	2.07	<.01	1.53	1.17	2.00	.002
Use of rituximab as maintenance vs induction only	0.93	0.40	2.16	.87	0.58	0.24	1.41	.23
Use of rituximab as combination (induction and maintenance) vs induction only	2.31	1.38	3.86	.87	1.86	1.10	3.16	.02
Usage of previous immunosuppression[†]	0.30	0.21	0.44	<.01	–	–	–	–
Age at last visit	1.03	1.02	1.04	<.01	–	–	–	–
Female vs male	1.29	0.90	1.84	.17	–	–	–	–
ANCA status (positive PR3, MPO, or both)	1.28	0.96	1.71	.09	–	–	–	–
Race	1.43	1.05	1.95	.02	1.53[‡‡]	1.08	2.16	.02
African Americans vs Caucasians	1.40	0.79	2.48	.26	–	–	–	–
Asians vs Caucasians	1.09	0.35	3.44	.88	–	–	–	–
Native Americans and others vs Caucasians	7.10	2.25	22.35	<.01	–	–	–	–

*Cyclophosphamide, methotrexate, leflunomide, and azathioprine.
[†]Adjusted for age at last visit follow-up, sex, race, ANCA status, previous immunosuppression use.
[‡‡]Adjusted for any rituximab dosing, age at last visit, sex, race, previous immunosuppression use, and ANCA status.

risk of developing Hypo-IgG, there have been different guidelines established for clinical monitoring.[18] Hypo-IgG was common in our cohort occurring in 42% of patients. In patients who received RTX for both induction and maintenance, the IgG nadir occurred after the induction course, and the levels remained stable/decreased during the maintenance phase. Hypo-IgG abnormalities are common in lupus nephritis[19] and other autoimmune disease,[20,21] and we theorize that Hypo-IgG may be more severe in AAV patients, particularly if they had RTX treatment because of the B-cell depletion. Many patients do not obtain routine immunologic evaluation before RTX therapy; thus, it can be difficult to determine whether underlying immune dysfunction was present at baseline or if the dysfunction is a long-lasting effect. In a recent cohort study in a tertiary referral center, of the 8,633 patients in the study, 85.4% (n = 38 245) did not have IgG levels checked prior to first RTX therapy.[15] In our study, 27.4% (n = 31) did not have IgG levels checked post-RTX therapy (visit 1). In our cohort, we observed 26% (n = 29) of the RTX-treated patients developed a decline in serum IgG to concentrations below 700 mg dL^{-1} and in 10% (n = 11) to concentrations below 500 mg dL^{-1}. Another study found significant decreased trend in both IgG and IgM (P = .023 and P = .043, respectively), but not in IgA (P = .124), 11 months post-RTX therapy after previous cyclophosphamide exposure.[10] Our study demonstrates that of those who developed moderate or severe Hypo-IgG, the nadir IgM was observed after clinical visit 2 or 3, similar to the trend in the nadir of IgG post-RTX therapy. Comparison of the first Ig measurement after RTX, repeat Ig measurements

from follow-up were not statistically significant ($P > .05$).

An observational study of 239 ANCA patients treated with RTX at Massachusetts General Hospital demonstrated that among the 50 patients who were included in both induction and maintenance groups, the mean within person decrease in IgG levels from the beginning of induction to the beginning of maintenance therapy was 226 mg dL^{-1} (95% CI, 155 to 298 mg dL^{-1}; $P < .001$). None of the patients with RTX induction had significant baseline Hypo-IgG (IgG < 400 mg dL^{-1}), compared with 9% of patients with RTX maintenance.[22] During maintenance therapy with prolonged RTX-induced continuous B cell depletion, total IgG levels remained essentially constant with a mean decline of 0.6% per year (95% CI, −0.2 to 1.4%), and the rate of serious infections was additionally relatively low in this group at 0.85 (95% CI, 0.66 to 1.1) per 10 patient years. Our study replicates the findings from this study. Similar to the findings of relatively stable IgG in our study, one study had 30 patients with GPA or MPA and 38 with connective tissue disease with median follow-up of 28 [IQR 6-131] months, where 11 cases (73.4%) developed Hypo-IgG that were transient and resolved spontaneously.[20] In contrast to this Italian study, our study is a relatively larger cohort, consisting of 113 AAV patients, and follow-up of 953 [IQR 1256] days, and demonstrated no severe adverse effects of infectious etiology resulting in mortality during the duration of the study. In addition, our study supports that the prior usage of immunosuppression is an independent predictor of developing Hypo-IgG, especially if patients were on high-dose steroids at the induction phase at visit 1.

Our study is not without limitations. This study was retrospective with limitations inherent with this design, and there was no control group. The small sample size allows for type II errors of not detecting significant differences, but we believe that with the rare nature of the disease, following any number of patients is important for results and understanding disease course. A major limitation is lack of baseline Ig levels on patients prior to start of therapy. We do note that the follow-up data may not be heavily affected by the missing data in this descriptive study, in part because of the diligent care of the providers for their patients who had AAV. Most patients enrolled in this Hopkins registry prefer to see their Hopkins providers regarding their AAV due to the rarity of the disease, complex disease course, complications, and need for specific management. In addition, there are other confounders that could impact the true nature of the Hypo-IgG, such as comorbid conditions, cumulative dosage of concurrent chemotherapy or other medications/immune modulators, duration of hospitalization, and renal replacement therapies. Future studies can evaluate the association with RTX effect and B cells, and assess antibody function (e.g., via vaccine responses), since these are not commonly performed in these patients but would provide significant additional information regarding humoral immunity. Since we analyzed patients from this single tertiary center, this may limit the generalizability of our results to other settings and demographics.

Conclusion

This observational study suggests that nadir IgG levels occur during induction dosing, and the IgG levels remain relatively stable or increase over time in those receiving maintenance RTX. While most patients had relatively stable IgG in moderate range over time after administration of RTX, those patients who developed low IgG post-RTX therapy were at risk of Hypo-IgG in subsequent visits.

Ethics Committee Approval: Ethical committee approval was received from the Johns Hopkins Institutional Review Board.

Informed Consent: Informed consent was not obtained due to the nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.T., A.Z., D.G.; Design - A.T., A.Z., A.A., D.G.; Supervision - A.T., D.G.; Resources - A.T., D.G.; Materials - A.T., A.A., P.S., D.G.; Data Collection and/or Processing - A.T., A.A., P.S., D.G.; Analysis and/or Interpretation - A.T., A.Z., A.A., P.S., D.G.; Literature Search - A.T., A.Z., A.A., D.G.; Writing Manuscript - A.T., A.A., P.S., D.G.; Critical Review - A.T., A.Z., A.A., P.S., D.G.

Declaration of Interests: The authors have no conflicts of interest to declare.

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References

1. Hamour S, Salama AD, Pusey CD. Management of ANCA-associated vasculitis: Current trends and future prospects. *Ther Clin Risk Manag*. 2010;6:253-264. [CrossRef]
2. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363(3):221-232. [CrossRef]
3. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010;363(3):211-220. [CrossRef]
4. Smith RM, Jones RB, Guerry MJ, et al. Rituximab for remission maintenance in relapsing anti-neutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2012;64(11):3760-3769. [CrossRef]
5. Miloslavsky EM, Specks U, Merkel PA, et al. Clinical outcomes of remission induction therapy for severe antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2013;65(9):2441-2449. [CrossRef]
6. Thiel J, Hassler F, Salzer U, Voll RE, Venhoff N. Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Arthritis Res Ther*. 2013;15(5):R133. [CrossRef]
7. Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypogammaglobulinemia: Incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun*. 2015;57:60-65. [CrossRef]
8. Marco H, Smith RM, Jones RB, et al. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. *BMC Musculoskelet Disord*. 2014;15:178. [CrossRef]
9. Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. *Clin Lymphoma Myeloma Leuk*. 2013;13(2):106-111. [CrossRef]
10. Venhoff N, Effelsberg NM, Salzer U, et al. Impact of rituximab on immunoglobulin concentrations and B cell numbers after cyclophosphamide treatment in patients with ANCA-associated vasculitides. *PLoS One*. 2012;7(5):e37626. [CrossRef]
11. Besada E, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: Results from a single Centre. *Rheumatology (Oxford)*. 2013;52(11):2041-2047. [CrossRef]
12. Besada E. Low immunoglobulin levels increase the risk of severe hypogammaglobulinemia in granulomatosis with polyangiitis patients receiving rituximab. *BMC Musculoskelet Disord*. 2016;17:6. [CrossRef]
13. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum*. 2006;54(9):2793-2806. [CrossRef]
14. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65(1):1-11. [CrossRef]
15. Barmettler S, Ong MS, Farmer JR, Choi H, Walter J. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. *JAMA Netw Open*. 2018;1(7):e184169. [CrossRef]
16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to

estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med*. 1999;130(6):461-470. [CrossRef]
17. StataCorp. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC, 2017.
18. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol*. 2017;139(3):S1-S46. [CrossRef]
19. Cuadrado MJ, Calatayud I, Urquizu-Padilla M, Wijetilleka S, Kiani-Alikhan S, Karim MY. Immunoglobulin abnormalities are frequent in patients with lupus nephritis. *BMC Rheumatol*. 2019;3(1):30. [CrossRef]
20. Padoan R, Felicetti M, Gatto M, Polito P, Doria A, Schiavon F. Rituximab-associated hypogammaglobulinaemia in ANCA-associated vasculitis and connective tissue diseases: A longitudinal observational study. *Clin Exp Rheumatol*. 2020;124(2):188-194.
21. Wade SK. Comparison of rituximab-associated hypogammaglobulinemia rates in patients with systemic rheumatologic conditions [abstract]. *Arthritis Rheumatol*. 2019;71(Suppl. 10)].
22. Cortazar FB, Pendergraft WF 3rd, Wenger J, Owens CT, Laliberte K, Niles JL. Effect of continuous B cell depletion with rituximab on pathogenic autoantibodies and total IgG levels in antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol*. 2017;69(5):1045-1053. [CrossRef]