Granulomatosis With Polyangiitis (Wegener's)
Impact of Maintenance Therapy Duration

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Abstract: To determine outcomes in relation to duration of maintenance therapy in patients with granulomatosis with polyangiitis (Wegener's) (GPA), we conducted a retrospective chart review of patients with GPA seen at a single vasculitis center from 1992 to 2010. All patients achieved remission defined by a Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS/WG) of 0 with either cyclophosphamide or methotrexate. After achieving remission all patients were started on maintenance therapy with either methotrexate or azathioprine.

The study comprised 157 patients with a median follow-up of 3.1 years. Using a univariate model, the continuation of maintenance medications for >18 months showed a 29% reduction in hazard ratio (HR) for relapse (HR, 0.71; 95% confidence interval [CI], 0.42–1.19; p = 0.19). Treatment for >36 months showed a 66% reduction in hazard ratio for relapse (HR, 0.34; 95% CI, 0.15–0.76; p = 0.008). When length of treatment was considered as a continuous factor, longer courses had an inverse relationship with the risk of relapse (HR, 0.70; 95% CI, 0.58–0.84; p < 0.001), which remained significant after adjusting for prednisone dose (HR, 0.59; 95% CI, 0.42–0.83; p = 0.003). Fifty-two percent of relapses occurred while the patients were off maintenance therapy. Among all patients who relapsed on therapy, 52% of those receiving methotrexate were on <15 mg/week, and 67% of those receiving azathioprine were on ≤50 mg/d. There were no differences between the short- and long-term maintenance therapy groups in overall adverse events or GPA-related morbidity.

Discontinuation or use of low doses of maintenance therapy is associated with a higher relapse rate.

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Abbreviations: ANCA = antineutrophil cytoplasmic antibody, AZA = azathioprine, BVAS/WG = Birmingham Vasculitis Activity Score for Wegener Granulomatosis, CI = confidence interval, CYC = cyclophosphamide, GPA = granulomatosis with polyangiitis, HR = hazard ratio, IV = intravenous, MMF = mycophenolate mofetil, MPA = microscopic polyangiitis, MPO = myeloperoxidase, MTX = methotrexate, PR3 = proteinase 3, RTX = rituximab.

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INTRODUCTION

Granulomatosis with polyangiitis (Wegener's) (GPA) is a systemic inflammatory disease histologically characterized by the presence of granulomas, necrosis, and vasculitis. While GPA typically affects the upper and lower respiratory tracts as well as the kidneys, any organ system can be involved. The disease has been associated with significant mortality and morbidity if untreated. Current treatment regimens lead to remission in up to 93% of patients.[2] Severe disease, defined as life- or critical organ-threatening illness, is initially treated with glucocorticoids and cyclophosphamide (CYC) or rituximab (RTX) to induce remission.[9,18] In mild to moderate disease, remission can be achieved with glucocorticoids and methotrexate (MTX). MTX has been shown to be as effective as CYC at inducing remission in this setting.[1] Despite high rates of remission, patients with GPA often experience relapses. This has led to longer treatment with agents such as MTX or azathioprine (AZA) to maintain remission.[3,7,14]

Over the last 50 years there has been a decline in mortality, relapse rate, and death related to therapy in GPA. This is likely due to changes in treatment strategies that include avoiding or limiting the duration of CYC use.[5] Results from recent prospective trials reveal relapse rates of 15%–35% at 12–18 month follow-up in patients continued on maintenance therapy.[7,14] However, higher frequencies of relapse are reported in the setting of withdrawal and discontinuation of therapy.[6,8]

Frequently, questions arise about when and if maintenance therapy can be safely discontinued following a prolonged period of remission. Published data addressing long-term outcomes in patients treated for >18 months are scant. To our knowledge, guidelines for duration of maintenance therapy for patients who never had a disease relapse do not exist. We conducted the current study to compare long-term outcomes in regard to duration and dose of maintenance immunosuppressive therapy in GPA patients without a history of relapse.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of newly diagnosed patients with GPA who received care at the Cleveland Clinic from January 1992 to August 2010. Patients were included only if they met all the following inclusion criteria: 1) met the 1990 American College of Rheumatology criteria for Wegener granulomatosis; 2) received induction therapy with CYC, RTX, or MTX at diagnosis; 3) achieved remission as defined as a Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS/WG) of 0;[17] 4) received initial maintenance therapy with either MTX or AZA (patients were not excluded if they were changed to mycophenolate mofetil [MMF] because of medication intolerance); 5) sustained remission for a period of at least 18 months, regardless of treatment duration, and 6) had adequate data available to determine dates of remission and relapse. "Maintenance therapy" was defined as treatment with AZA, MTX, or MMF after patients achieved remission. Patients were excluded if maintenance therapy was not started for >1 month after the date of remission.

Remission was defined as a BVAS/WG score of 0, and relapse was defined as a score of ≥1, after a period of remission. Patient information was gathered from onset of initial symptoms until remission was achieved after the first relapse or until the last follow-up. Patients on maintenance therapy for >18 months were categorized as the "long-term maintenance group," while those receiving maintenance therapy for ≤18 months were categorized as the "short-term maintenance group." A separate analysis was performed for patients on maintenance therapy for 18–36 months and for those treated for >36 months.

Adverse events included those attributed to medications for the treatment of GPA. Serious adverse events were defined as those that were life threatening, required hospitalization, or resulted in death. Infections requiring antibiotics or hospitalization and chronic organ damage related to GPA were recorded.

This study received approval from the ethics committee of the Cleveland Clinic Foundation. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Numerical measures were summarized by median values and quartiles. Categorical values were summarized by frequency and percentage. Univariable comparisons were conducted using Wilcoxon rank sum test for numerical values and either a chi-square test or Fisher exact test (where appropriate). Significance was determined by a p value ≤ 0.05. Duration of relapse-free remission was evaluated using cox proportional hazard models. Three models were constructed to illustrate the effect of duration of maintenance therapy on time to relapse. The first model used duration of maintenance therapy as a categorical factor, comparing fewer than 18 months of therapy to more than 18 months of therapy. The second model used duration of therapy as a continuous factor, eliminating the arbitrary dichotomy of less than or equal to and more than 18 months. The third model adjusted the continuous duration of therapy for prednisone as a time-dependent covariate.

RESULTS

We reviewed 797 GPA patient records from the period January 1992 to August 2010. All of these patients were seen by 3 physicians within the Center for Vasculitis Care and Research at the Cleveland Clinic (CAL, GSH, AVF). We excluded 229 patients because of relapse before 18 months following induction of remission, and 8 patients because they started maintenance therapy >1 month after remission was achieved. A total of 157 patients met all of the inclusion criteria (Figure 1).

The median age at diagnosis was 46 years (range, 12–83 yr). Eighty-eight percent of patients were white. The duration of follow-up was a median of 3.1 years (range, 18 mo to 16.8 yr). The mean BVAS/WG score at diagnosis was 7.0 (range, 1–20). There were no differences between the short- and long-term treatment groups regarding initial organ manifestations, initial dose of maintenance therapy, antineutrophil cytoplasmic antibody (ANCA) status (myeloperoxidase [MPO] or proteinase 3 [PR3]), or BVAS/WG scores at diagnosis (Table 1).

Induction Therapy

Although we did not exclude patients who received RTX for initial induction therapy, none of these patients met the inclusion criteria. More patients in the long-term follow-up group received CYC as induction therapy than in the short-term follow-up group (83% vs. 56%, respectively; p = 0.007) (see Table 1). The mean duration of CYC use in the overall cohort was 9.3 months (9.4 mo in long-term group vs. 8.3 mo in the short-term group).

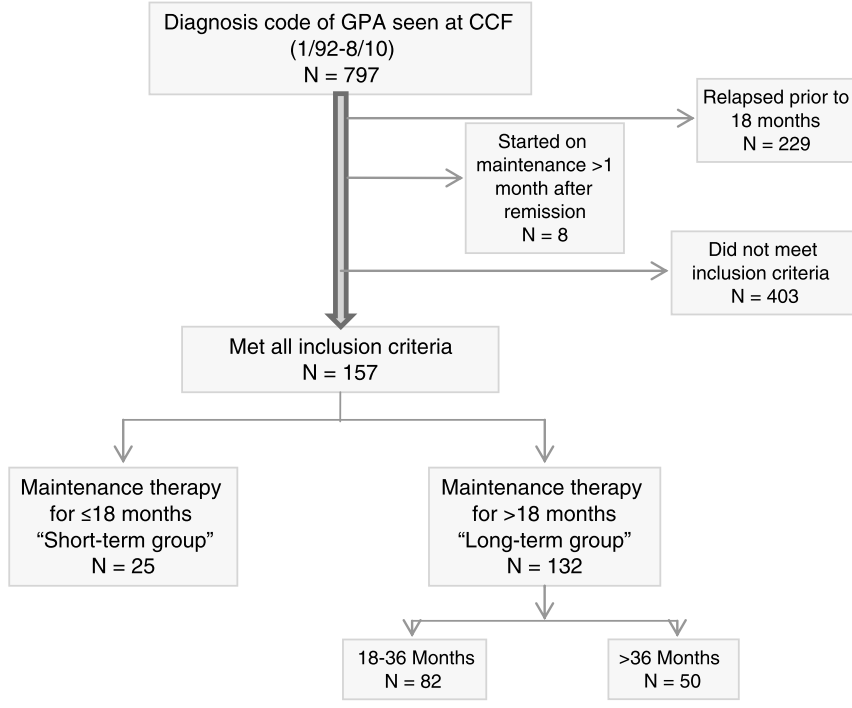
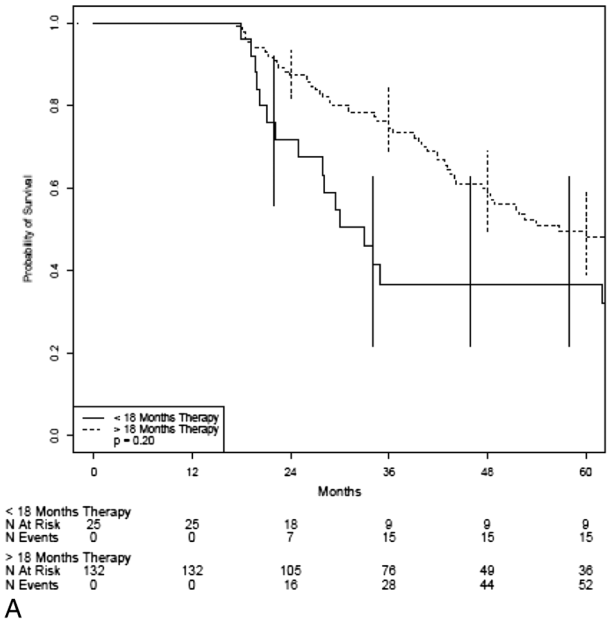


FIGURE 1. Cohort diagram. Patients were initially excluded if they relapsed before 18 months. One hundred fifty-seven patients met all the inclusion and exclusion criteria. Patients were then divided based on duration of maintenance therapy (≤ or >18 months). The long-term group was further divided into patients on maintenance between 18 and 36 months and those who received maintenance therapy for >36 months.

TABLE 1. Baseline Characteristics

	Short-Term Maintenance Therapy (N = 25)			Long-Term Maintenance Therapy (N = 132)		
	Total	N	Statistics	N	Statistics	P
Age[a]	157	25	48.77 [31.9, 57.1]	132	46.23 [30.68, 54.67]	0.59[W]
Sex[b]						0.30[C]
Female	70	14	56	56	42.42	
Male	87	11	44	76	57.58	
Ethnicity[b]						
White	139	22	88	117	88.64	> 0.99[F]
BVAS/WG at diagnosis[a]	157	25	6 [4, 7]	132	7 [4, 10]	0.066[W]
IV steroids given at diagnosis[b]	34	2	12.5	32	32.32	0.14[F]
Prednisone at remission (mg/day)[a]	94	11	17.5 [7.5, 25]	83	20 [10, 30]	0.61[W]
Drug used for induction therapy[b]						0.007[F]
CYC	123	14	56	109	82.58	
RTX	0	0	0	0	0	
MTX	34	11	44	23	17.42	
Initial maintenance drug[b]	157					0.52[C]
AZA	56	7	28	49	37.12	
Dose (mg/day)[a]	48	4	125 [87.5, 150]	44	100 [93.75, 150]	0.92[W]
MTX	101	18	72	83	62.88	
Dose (mg/week)[a]	71	11	20 [15, 20]	60	15 [15, 20]	0.24[W]
Patients changed to different maintenance drug during maintenance therapy[b]						
AZA to MTX[b]	4	0	0	4	3.03	> 0.99[F]
MTX to AZA[b]	7	0	0	7	5.3	0.60[F]
MTX or AZA to MMF[b]	10	2	8	8	6.06	0.66[F]
Cr at diagnosis[a]	23	3	1.1 [1, 2.75]	20	0.9 [0.88, 1.35]	0.38[W]
Kidney failure at diagnosis (Cr > 2)[b]	5	1	4	4	3.03	0.82[C]
Cr at remission[a]	68	2	0.85 [0.72, 0.98]	66	1 [0.8, 1.4]	0.34[W]
ANCA positive[b]	122	19	86.36	103	82.4	0.77[F]
PR3 positive[b]	87	13	52	74	56.06	0.88[C]
MPO positive[b]	9	2	8	7	5.3	0.64[F]
Manifestations at diagnosis[b]						
ENT	136	23	92	113	85.61	0.53[C]
Lung	114	16	64	98	74.24	0.33[C]
Nodules	59	11	44	48	36.36	0.62[C]
Aveolar hemorrhage	37	3	12	34	25.76	0.22[C]
Subglottic stenosis	8	0	0	8	6.06	0.44[C]
Eye	29	4	16	25	18.94	0.95[C]
Skin	38	9	36	29	21.97	0.21[C]
Constitutional	47	5	20	42	31.82	0.34[C]
Glomerulonephritis	88	14	56	74	56.06	0.83[C]
CNS	6	1	4	5	3.79	0.60[C]
Peripheral neuropathy	16	2	8	14	10.61	0.97[C]
Heart	1	0	0	1	0.76	0.35[C]

[a]Median [P25, P75]; [b]Percentage.
C: Pearson chi-square test with Yates continuity correction.
F: Fisher exact test for count data.
N: Number.
W: Wilcoxon rank sum test with continuity correction.
MTX: Methotrexate.
AZA: Azathioprine.
CYC: Cyclophosphamide.
RTX: Rituximab.
Cr: Creatinine (mg/dL).



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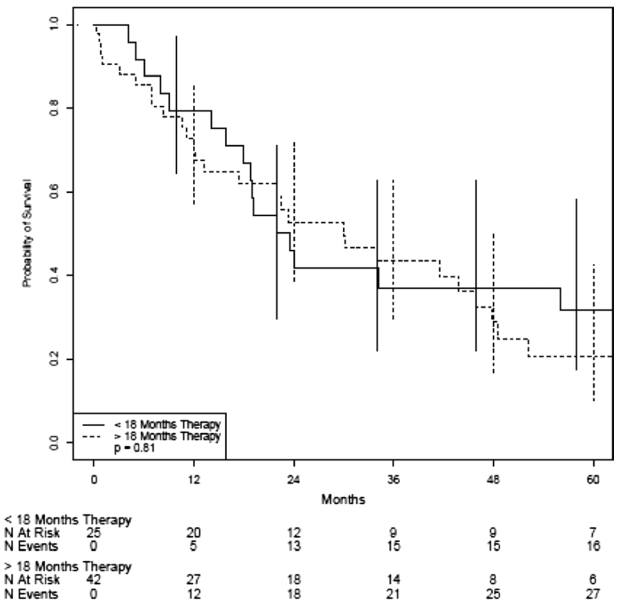

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FIGURE 2. A) Relapse-free interval from start of maintenance therapy. B) Relapse-free interval from discontinuation of maintenance therapy, excluding patients who relapsed while on maintenance therapy.

Maintenance Therapy

At remission, there were no differences between the short- and long-term treatment groups in regards to prednisone dose, choice of maintenance drug, or dose of maintenance drug. Ninety-six percent of patients were started on maintenance therapy at the time of remission. In 7 patients there was a delay of up to 4 weeks in the onset of maintenance therapy following remission. In 3 of these patients maintenance therapy was started within 2 weeks of remission. The most common reason for delay in starting maintenance therapy was recovery from leukopenia produced during induction of remission (3 patients). The median duration of maintenance therapy in the short-term group was 11.5 months (range, 0.3 to 17.4 mo), and the median duration in the long-term group was 32 months (range, 18.1 to 115.1 mo). Twenty-one patients were changed from 1 maintenance drug to another, most commonly as a result of medication-related side effects (74%).

Relapse

Overall, 91 patients (58%) relapsed during follow-up. Nineteen patients relapsed in the short-term group (76%), and 72 in the long-term group (55%). MTX treatment was associated with a higher subsequent relapse rate compared with CYC when used for induction therapy (HR, 1.77; 95% CI, 1.75–1.80; p = 0.013).

When duration of treatment was compared using a univariable model, patients on more than 18 months of maintenance therapy showed a 29% reduction in hazard for relapse compared to patients with <18 months of therapy (HR, 0.71; 95% CI, 0.42–1.19; p = 0.19). At 36 months there were significantly fewer relapses in those patients on maintenance therapy for >18 months, as shown in Figure 2a. A second plot shows the relapse-free interval from the discontinuation of maintenance therapy to relapse (Figure 2b). Unlike the first plot, this shows no noticeable difference between groups, indicating that the time to relapse is similar once patients discontinue maintenance therapy.

An analysis of patients treated for longer than 36 months compared with those treated for shorter periods of time (Figure 3) showed that patients treated for longer than 36 months had a 66% lower risk of relapse (HR, 0.34; 95% CI, 0.15–0.76; p = 0.008). Median time to relapse was 33.0 months in the short-term group (range, 18.2–125.4 mo), 43.5 months in those treated from 18 to 36 months (range, 18.1–201.6 mo), and 74.5 months for those treated for >36 months (range, 36.0–115.1 mo). When duration of treatment was analyzed as a continuous factor, it was inversely related to risk of relapse, indicating that longer

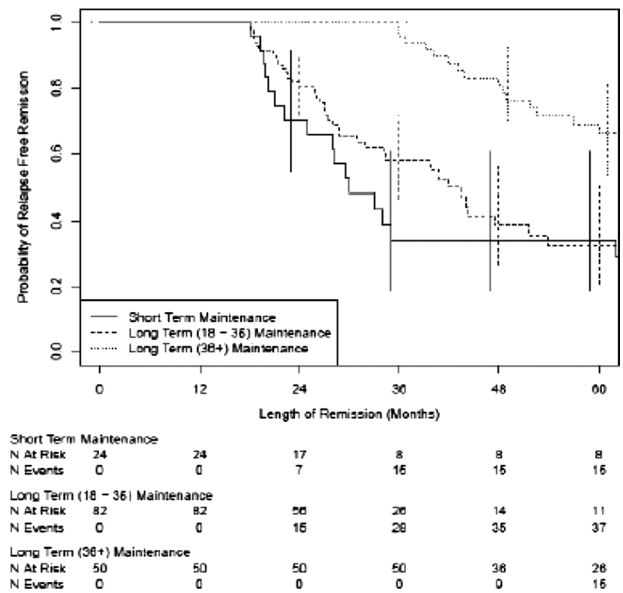

FIGURE 3. Kaplan-Meier curves for relapse-free remission for GPA patients based on duration of maintenance therapy: <18 months, 18–36 months, and >36 months.

maintenance therapy reduces the risk for relapse (HR 0.7; 95% CI, 0.58–0.84; p ≤ 0.001). After adjusting for prednisone use, duration of maintenance therapy continued to show a significant inverse relationship with risk of relapse (HR, 0.59; 95% CI, 0.42–0.83; p = 0.003). The probability of relapse at any given time point was higher in those patients on maintenance therapy for shorter periods of time (results not shown).

Univariable analysis revealed that none of the following was a significant risk factor for relapse: BVAS score at diagnosis, ANCA positivity, type of ANCA antigen per ELISA (PR3 or MPO), or IV methylprednisolone use.

In those patients who eventually relapsed there was no difference in disease severity (as measured by BVAS/WG) or renal function at relapse between the short-term and long-term treatment groups. There were also no statistically significant differences in time to achieve remission again (median, 131 d for short-term vs. 98 d for long-term treatment groups; p = 0.22), in the frequency of glomerulonephritis at relapse between groups (58% for short-term vs. 35% for long-term treatment groups; p = 0.11), or in other manifestations at relapse between the 2 groups (Table 2). Forty-eight patients relapsed while off of maintenance therapy (53% of all patients that relapsed). Of those patients receiving MTX at relapse, 51.9% were taking <15 mg per week. Of those patients on AZA, 67% were taking 50 mg or less per day at the time of relapse. The median doses at the time of relapse were 50 mg daily (range, 25–100 mg/d) for AZA, 15 mg/week (range, 5–22.5 mg/wk) for MTX, and 2000 mg/d (range, 1500–2500 mg/d) for MMF.

Glucocorticoids

Intravenous (IV) pulse methylprednisolone was given to 28% of 123 patients for whom such data were available at diagnosis. There was no significant difference between the percentage of patients who initially received IV pulse methylprednisolone in the long-term (32%) compared with the short-term treatment group (12.5%). All patients received daily oral prednisone at onset of treatment. The mean initial daily prednisone dose was 62 mg daily (data available for 109 patients). While prednisone tapering was at the discretion of the treating physician, a similar tapering approach is used by each. This includes weekly tapering in decrements of 5 mg with a goal dose of 20 mg/d at 3 months. Upon achieving a dose of 20 mg/d of prednisone without relapse, tapering was slowed to weekly decrements of 2.5 mg until the patient achieved a dose of 10 mg/d. Then the prednisone was tapered by 1 mg weekly with a goal of achieving a dose of 5 mg/d or less by 6–9 months. The average prednisone dose at remission was 17.5 mg/d in the short-term group and 20 mg/d in the long-term group. Of those patients who relapsed, 16% of patients in the short-term group and 22% of patients in the long-term group were still receiving glucocorticoids (median dose of 0 in both groups).

Adverse Events/Morbidity

There were no differences between the short-term and long-term maintenance therapy groups in the number of overall medication-related adverse events. Thirty-two medication-related

TABLE 2. Manifestations at Relapse

	Short-Term Maintenance Therapy (N = 19)			Long-Term Maintenance Therapy (N = 72)		
	Total	N	Statistics	N	Statistics	P
Cr[b]	20	7	0.91 [0.76, 1.1]	13	1.1 [0.9, 1.2]	0.38[W]
BVAS/WG[b]	90	20	3 [2, 4.25]	70	3 [2, 5]	0.64[W]
Days to second remission[b]	58	12	130.5 [83.75, 277]	46	97.5 [64.5, 141.5]	0.22[W]
On prednisone at relpase[a]	19	3	15.79	16	22.22	0.75[F]
Dose of prednisone (mg/d)[c]	71	14	0 [0, 30]	57	0 [0, 15]	0.91[W]
Manifestations[a]						
ENT	45	10	52.63	35	48.61	0.80[F]
Lung	41	6	31.58	35	48.61	0.21[F]
Nodules	23	4	21.05	19	26.39	0.77[F]
Aveolar hemorrhage	10	3	15.79	7	9.72	0.43[F]
Subglottic stenosis	9	1	5.26	8	11.11	0.68[F]
Eye	12	1	5.26	11	15.28	0.45[F]
Skin	5	0	0	5	6.94	0.58[F]
Constitutional	5	0	0	5	6.94	0.58[F]
Glomerulonephritis	36	11	57.89	25	34.72	0.11[F]
CNS	4	1	5.26	3	4.17	>0.99[F]
Peripheral neuropathy	4	2	10.53	2	2.78	0.19[F]
Heart	2	0	0	2	2.78	>0.99[F]

[a]Percentage; [b]Median [P25, P75]; [c]Median [Min, Max].

F: Fisher exact test for count data.

N: Number.

W: Wilcoxon rank sum test with continuity correction.

Cr: creatinine (mg/dL).

hemocytopenic events occurred (leukopenia in 28, thrombocytopenia in 1, and anemia in 3) (12% in short-term group and 22% in long-term group; p = 0.52). Twenty-nine of these events (91%) were cases of mild hemocytopenia that resolved with a minor change in the dose of medication. Three hemocytopenic events required intervention: 2 episodes of leukopenia requiring granulocyte colony-stimulating factor and 1 episode of anemia requiring transfusion (all occurring in the long-term group). There were 7 severe infections, which all occurred in the long-term group during maintenance therapy (5% of long-term group vs. 0% in short-term group). Severe infections included pneumonia in 5 cases, empyema in 1, and cytomegalovirus in 1. There was a higher rate of drug-induced transaminase increases in the short-term group, and the majority occurred during treatment with MTX (20% vs. 5.3%; p = 0.025). (Table 3) There was no significant difference in morbidity related to GPA between the short-term and long-term maintenance therapy groups (Table 4).

DISCUSSION

Results from the current study indicate that among newly diagnosed patients with GPA, a longer duration of maintenance therapy is associated with fewer relapses. Medications used in to maintain remission (MTX or AZA) are generally well tolerated. Relapses are common in patients with GPA, as emphasized by our data, and can occur in patients on maintenance therapy. Our data suggest that the dosage of maintenance medications is an important factor in sustaining remission.

We focused on a subset of GPA patients, namely patients with newly diagnosed disease who had sustained remission for at least 18 months. There are several reasons to focus on this group. First, in GPA patients who have had numerous relapses, it is generally thought that there is a higher risk of subsequent relapses. In this situation maintenance medications, as long as they are well tolerated, are often continued indefinitely in the absence of toxicity. Because decision-making about duration of maintenance therapy is less clear in newly diagnosed GPA, we included only those patients in this study. Second, prior data from prospective studies have supported continuing maintenance therapy for up to 18 months. Because of the lack of data on continuation of maintenance therapy beyond 18 months, we evaluated the relapse rates in patients treated for >18 months compared with those treated for ≤18 months. Patients were included in this study only if they sustained remission for at least 18 months. This was done to prevent a better relapse-free survival in the long-term treatment arm simply because by definition patients had to be relapse-free for at least 18 months (mortality bias).

There are minor differences between our cohort of patients and those previously reported in large cohort trials.[1,3,7,14] Our short- and long-term treatment groups each achieved excellent initial results, but relapses progressively increased with tapering and discontinuation of maintenance therapies. Our overall relapse rate by 18 months was 29%, which is comparable to that previously reported by Jayne et al[7] and Pagnoux et al[14] (15%–40%). A much

TABLE 3. Adverse Events

	Short-Term Maintenance Therapy (N=25)			Long-Term Maintenance Therapy (N=132)		
	Total	N	Statistics	N	Statistics	P
Number of adverse events[a]	68	10	0 [0.2]	58	0.5 [0, 71]	0.25[W]
Number of patients with adverse event[b]	32	3	12	29	21.97	0.38[C]
Serious adverse events[b]	17	2	8	15	11.36	>0.99[F]
Severe infection[b]	7	0	0	7	5.3	0.60[F]
Cytopenias requiring intervention[b]	3	0	0	3	2.27	0.97[C]
Nausea[b]	10	2	8	8	6.06	0.66[F]
Emesis[b]	1	0	0	1	0.76	>0.99[F]
Gonadal failure[b]	3	0	0	3	217	>0.99[F]
Hair loss[b]	2	0	0	2	1.52	>0.99[F]
Cystitis[b]	4	0	0	4	3.03	>0.99[F]
Steroid psychosis[b]	1	0	0	1	0.76	>0.99[F]
Osteoporosis with fracture[b]	5	0	0	5	3.79	>0.99[F]
Cataracts[b]	4	0	0	4	3.03	>0.99[F]
New-onset diabetes[b]	5	1	4	4	3.03	0.59[F]
Malignancy[b]	8	1	4	7	5.3	>0.99[F]
Avascular necrosis[b]	6	0	0	6	4.55	0.59[F]
Rash[b]	5	8	3	2.27	0.18[F]	
Drug-induced elevation inAST/ALT[b]	12	5	20	7	5.3	0.025[F]
Steroid-induced myopathv[b]	4	0	0	4	3.03	0.99[F]
Drug-induced fever[b]	2	0	0	1.52	0.99[F]	
Drug-induced fatigue requiring discontinuation[b]	2	0	0	1.52	0.99[F]	

[a]Median [Min, Max]; [b]Percentage.

C: Pearson chi-square test with Yates continuity correction.

F: Fisher exact test for count data.

N: Number.

W: Wilcoxon rank sum test with continuity correction.

TABLE 4. Morbidity

	Short-Term Maintenance Therapy (N=25)			Long-Term Maintenance Therapy (N=132)		
	Total	N	Statistics	N	Statistics	P
Chronic kidney disease[a]	10	1	4	9	6.82	>0.99[F]
End-stage renal disease[a]	6	1	4	5	3.79	>0.99[F]
Lung fibrosis[a]	3	1	4	2	1.52	0.41[F]
Tracheal damage[a]	2	0	0	2	152	>0.99[F]
Sinus and nasal damage[a]	3	1	4	2	1.52	0.41[F]
Saddle nose deformity[a]	7	2	8	5	3.79	0.31[F]
Peripheral neuropathy[a]	7	1	4	6	4.55	0.99[F]
Subglottic stenosis[a]	5	1	4	4	3.03	0.59[F]
Proptosis[a]	1	0	0	1	0.76	43.99[F]
Vision loss[a]	1	0	0	1	0.76	0.99[F]
Cranial nerve palsy[a]	1	0	0	1	0.76	0.99[F]
Gangrene	1	0	0	1	0.76	0.99[F]
Other morbidity[a]	15	1	4	14	10.61	0.47[F]

[a]Percentage.
F: Fisher exact test for count data.
N: Number.

higher relapse rate was reported by De Groot et al,[1] but in that study maintenance therapy was discontinued by 12 months. Consistent with this observation, most relapses in the current study occurred after the patient stopped maintenance therapy (52%). Our study reports the results of an observational cohort studied retrospectively. The other studies were prospective randomized trials and many included patients with microscopic polyangiitis (MPA), which is known to relapse less frequently than GPA and may contribute to in-study differences in relapse rates. The mean age at diagnosis in our cohort was 46 years. This is younger than that reported in several other studies[1,3,8,14] and reflects the fact that pediatric patients were included in our study.

Our results are supported by 3 analytical models that evaluate duration of therapy as a categorical variable, duration of therapy as a continuous variable, and probability of relapse over time based on treatment duration (6, 12, 18, 24, or 36 months). Both the duration and dose of glucocorticoids can have a major impact on relapse rate. In the categorical model glucocorticoids are unlikely to have affected the results, as the number of patients receiving IV pulse methylprednisolone and daily doses of prednisone at remission and at relapse were not different between the short-term group and the long-term group. In the other models, adjustment for prednisone did not change the results.

The results from the current study suggest that the dose of maintenance therapy is an important factor that affects the relapse rate. Protocols initially designed at the National Institutes of Health (NIH) for the treatment of GPA with MTX demonstrated efficacy with doses of 15–25 mg/week and increasing frequency of relapses with tapering below 15 mg/week.[4,11,16] Studies with AZA demonstrated efficacy with 2 mg/kg per day, later reducing to 1.5 mg/kg per day. Consistent with prior studies, the majority of patients who relapsed did so while the maintenance drug dose was being decreased or stopped.[1,19] These findings emphasize the need not only to continue maintenance therapy for extended periods, but also to treat using doses proven to be efficacious, as long as they are well tolerated.

Medication adverse events are important to consider when weighing the risks versus benefits of any prolonged therapy. There was no difference between the short- and long-term maintenance therapy groups in regard to overall treatment-associated adverse events. However, it should be recognized that the current study was not powered to see a difference in adverse events. Eight to 11% of patients had severe adverse events, with no difference between groups. There was no statistical difference in the rate of severe infections between groups, although this should be considered as a possible concern that could become more apparent with larger numbers of patients studied over longer periods of time. Nonetheless, it appears that over the time periods covered by our study, the benefit of reducing relapse, and its resultant disease-related morbidity, may outweigh the risks of long-term maintenance therapy with the agents employed. This is especially true when considering that over half the patients in the short-term group demonstrated organ-threatening disease at relapse including alveolar hemorrhage, glomerulonephritis, or nervous system involvement.

There are several limitations to the current study that should be acknowledged. First, this is an observational cohort of patients studied retrospectively. Second, mortality bias is a potential limitation of retrospective studies. Mortality bias refers to the fact that patients in longer treatment arms were able to survive relapse in order to be a part of that treatment arm. This bias is less of a concern when comparing patients on maintenance therapy for greater or less than 18 months as all patients were required to sustain remission for at least 18 months. A mortality bias is a greater concern in analyses either including a subgroup treated for >36 months or evaluating the duration of maintenance therapy as a continuous variable. Third, the general practice at our institution has been to continue maintenance therapy for >18 months, leading to a small sample size within the short-term group (n = 25, 16% of cohort). Therefore, our study was not powered to see a significant difference in regards to adverse events between groups. However, in general the doses of MTX and AZA used for maintenance therapy are well tolerated in a number of other diseases and need to be weighed against the potential mortality and morbidity associated with relapse. Finally, lack of randomization resulted in a significantly higher percentage of patients in the long-term

group receiving CYC for initial induction therapy, which could be a potential confounder of these results. We were not able to adjust for the type of induction therapy using a multivariable model because of the limited number of events. However, the time to relapse after discontinuation of maintenance therapy was not different among groups (see Figure 2b). This suggests that long-lasting effects from induction therapy did not affect the relapse rate, and the withdrawal of any effective maintenance agent, regardless of treatment provided to induce remission, has a high risk of later relapse. Although MTX treatment was associated with a higher subsequent relapse rate compared to CYC when used for induction therapy, caution should be exercised when interpreting these results as MTX has been shown to be an effective remission-induction agent in appropriate patients,[1] and experience from the NIH[4,11,16] and our center[19] has confirmed these observations. The long duration of CYC exposure seen in this cohort is explained by the fact that many of the patients completed induction therapy before being seen at our institution. Our results need be confirmed by prospective trials that address the limitations inherent in a retrospective design.

RTX was recently shown to be not inferior to CYC as an induction agent.[9,18] While we did not exclude patients induced with RTX, none of these patients met all our inclusion criteria for several reasons. First, many of the patients were seen before the publications documenting efficacy of RTX. Second, before the current study was performed, there were no reported data regarding effective maintenance therapy after treatment with RTX. Therefore, many of our patients who received RTX for induction therapy were not started on MTX or AZA for maintenance therapy or were started >1 month after remission. Thus the results of this study can not be reliably applied to this subgroup of patients.

Not excluding patients on MMF for maintenance therapy could be viewed as a limitation. Use of MMF as a maintenance agent has been supported by smaller trials.[6,10,12,13,15] In 2010, Hiemstra et al[3] found MMF to be less effective than AZA in maintaining remission in GPA and MPA. Because only 10 patients in the current cohort were treated with MMF (after intolerance or contraindications to MTX or AZA), we are unable to draw conclusions about its efficacy for maintenance therapy. Exclusion of these patients is unlikely to have affected our overall results.

Including patients not immediately started on maintenance therapy after the end of induction therapy could also be considered a weakness. Any patient who was not started on maintenance therapy within 1 month of remission was excluded in our study. The vast majority of the patients in this study were started on maintenance therapy at remission (96%). Hemocytopenia (commonly leukopenia) was the most common cause for delay in the initiation of maintenance therapy. As this is a situation that occurs occasionally in clinical practice, this should not be considered a weakness of this study.

Compared to several prospective trials, the current study has several strengths. This study included a relatively large number of patients. This was a single center study in which all the patients were seen by 1 of 3 vasculitis experts who share similar strategies for the care of GPA patients. This study included only patients with GPA, which differs from many other studies that included patients with other forms of small vessel vasculitis, especially MPA. MPA is known to be associated with fewer relapses compared with GPA. This cohort also included pediatric patients, who are less prone to GPA, but are still a very clinically relevant population.

CONCLUSIONS

GPA is a life-threatening disease for which outcomes have greatly improved over the past 50 years. While new therapies have proven to be life saving, they are not curative. Relapses are common especially after therapy has been tapered and discontinued. Relapses may be associated with incremental morbidity and even mortality. Current maintenance medications are generally well tolerated. Based on this study there appears to be a strong inverse relationship between the length of maintenance therapy and the relapse rate. The dose of maintenance medications is an important factor in relapses, with the majority of relapses occurring at doses generally considered to be subtherapeutic.

These results show that until curative therapies are discovered, patients with GPA will have improved outcomes if they receive long-term maintenance therapy. In this study, such therapy decreased the risk of disease relapse and its associated morbidities.

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