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Improving clinical management in ANCA-associated vasculitis

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Extended versus Standard Azathioprine Maintenance Therapy in Newly Diagnosed Proteinase-3 Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis Patients who Remain C-ANCA Positive after Induction of Remission: A Randomized Clinical Trial.

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ABSTRACT

Background

Cytoplasmic anti-neutrophil cytoplasmic antibody (C-ANCA) positivity at remission has been associated with an increased relapse rate in patients with proteinase-3 anti-neutrophil cytoplasmic antibody associated vasculitis (PR3-AAV) after a switch to azathioprine maintenance therapy. We therefore hypothesized that extended azathioprine maintenance therapy could reduce the incidence of relapse in this setting.

Methods

Patients newly diagnosed with PR3-AAV at 12 centers in The Netherlands during 2003-11 who received a standardized induction regimen consisting of oral cyclophosphamide and corticosteroids were enrolled (n=131). Patients were randomized to standard or extended azathioprine maintenance therapy when C-ANCA was positive at the time of stable remission. Standard maintenance treatment consisted of azathioprine (1.5-2.0 mg/kg) until one year after diagnosis and subsequent tapering to 25 mg every 3 months. Extended azathioprine maintenance therapy (1.5-2.0 mg/kg) was continued until 4 years after diagnosis and tapered thereafter. The primary endpoint was relapse-free survival at 4 years after diagnosis.

Results

In patients with PR3-AAV who were C-ANCA positive at the time of stable remission, relapse-free survival at 4 years after diagnosis did not differ significantly between standard azathioprine (n= 24) and extended azathioprine (n= 21) maintenance therapy (P= 0.40). There was also no significant difference in relapse-free survival between patients receiving standard azathioprine (n= 106) versus extended azathioprine maintenance therapy (n= 21; P=0.94). In addition, there was no difference in relapse rate between patients with PR3-AAV who were C-ANCA positive (n= 45) at the time of remission versus patients who became C-ANCA negative at the time of remission (n= 82; P=0.62).

Conclusions

This randomized trial suggests that extended azathioprine maintenance therapy has only a limited effect on the prevention of relapse in patients with PR3-AAV at 4 years after diagnosis. Moreover, positive C-ANCA status at stable remission was not associated with an increased rate of relapse.

Trial registration

clinicaltrials.gov. Identifier NCT 00128895

INTRODUCTION

Granulomatosis with polyangiitis (GPA, previously called Wegener's granulomatosis) and microscopic polyangiitis (MPA) are small-vessel vasculitides frequently associated with antineutrophil cytoplasmic antibody (ANCA) (1). In the majority of patients with so-called ANCA-associated vasculitis (AAV), disease remission can be induced by treatment with cyclophosphamide and corticosteroids or, as shown more recently, with rituximab and corticosteroids. Higher cumulative doses of cyclophosphamide are associated with considerable toxicity, and therefore the current standard of care is a stepwise approach comprising cyclophosphamide induction therapy followed by a less toxic maintenance agent, preferably azathioprine or methotrexate, for at least 18 months after diagnosis (2-4). However, the optimal duration of this maintenance therapy is unknown and a substantial number of patients experience disease relapse within 5 years after diagnosis. These relapses are associated with considerable morbidity and mortality (5-7), and avoidance of relapse via patient-tailored maintenance therapy would be highly preferable.

Several studies have shown that patients positive for proteinase 3 (PR3)-ANCA are more prone to relapse during long-term follow-up compared with myeloperoxidase (MPO)-ANCA positive patients (8,9). Additionally, in a retrospective study, we previously observed that in patients with PR3-ANCA associated vasculitis, positive cytoplasmic (C)-ANCA at the time of a switch to azathioprine following successful induction with cyclophosphamide is associated with a significantly increased risk for relapse during long-term follow-up (10). Therefore, we hypothesized that in patients with PR3-AAV, positive C-ANCA after induction of stable remission is associated with an increased risk of relapse and that these patients may benefit from extended azathioprine maintenance therapy. Here, we report the results of a randomized multicentre clinical trial ('AZA-ANCA') to evaluate the efficacy and safety of extended azathioprine maintenance therapy in patients with PR3-AAV who remain C-ANCA positive after induction of remission by therapy including oral cyclophosphamide.

METHODS

The 'AZA-ANCA trial was conducted at 12 hospitals in The Netherlands between June 2003 and October 2014. The study protocol was reviewed and approved by the medical ethical committee of the University Medical Center Groningen (UMCG) and the participating centres (no 2002/213).

Consecutive patients with newly diagnosed PR3-ANCA associated vasculitis who were treated with cyclophosphamide and prednisolone induction therapy were recruited. All participants were > 18 years of age and provided written informed consent.

Exclusion criteria were intolerance for azathioprine, or inability to give informed consent. Patients were withdrawn in the event of failure to control progressive disease using the induction protocol or for failure to achieve remission within 6 months after diagnosis.

Patients were enrolled between diagnosis and remission. After 3 months of remission, defined as 'stable remission', when therapy was switched to azathioprine, C-ANCA status was determined in a central laboratory at the UMCG by indirect immunofluorescence (IIF) (11). Patients who were C-ANCA positive (IIF \geq 1: 40) were randomized in a 1:1 ratio to receive standard or extended azathioprine maintenance therapy. Patients who were C-ANCA negative at the time of stable remission were all treated according to the standard regimen with azathioprine maintenance therapy and decreasing doses of prednisolone.

Drug regimen and treatment protocol

All patients received oral cyclophosphamide (2 mg/kg) and prednisolone (1 mg/kg) for the induction of remission. Additionally, intravenous methylprednisolone pulses and/or plasmapheresis were permitted when indicated according to clinical judgement. Dosages of cyclophosphamide were adjusted to maintain the leukocyte count above 4×10^9 /liter. At 4-6 weeks after start of therapy, the daily prednisolone dosage was tapered by 10 mg every 2 weeks until 30 mg/day and thereafter decreased by 5 mg every 2-4 weeks. When the dose of prednisolone was 15 mg, it was tapered by 2.5 mg every 2 weeks. Steroids were stopped at week 28- 34 after diagnosis.

After remission had been sustained for 3 months ('stable remission'), patients were switched to azathioprine (1.5-2 mg/kg). The dose of azathioprine was adjusted to maintain the leukocyte count above 4×10^9 /L. In the standard treatment arm, whether for C-ANCA negative patients or for C-ANCA positive patients randomized to receive standard azathioprine therapy, 1 year after diagnosis azathioprine was tapered by 25 mg every 3 months, resulting in a total treatment duration of approximately ~24-30 months. In the C-ANCA- positive group, patients randomized to the extended azathioprine arm continued to receive azathioprine at a dose of 1.5-2 mg/kg until 4 years after diagnosis, thereafter tapered by 25 mg every 3 months until discontinuation.

During treatment, all patients received prophylaxis against *Pneumocystis jirovecii* pneumonia (480 mg co-trimoxazol daily or 960 mg co-trimoxazol every other day). Prophylactic therapy against candidiasis and osteoporosis was given according to local practice.

Patient evaluation and outcomes

Patients were evaluated at the time of diagnosis, at the point of switch to azathioprine (i.e. at 'stable remission'), at 12 months and then every 3 months until the end of the study.

At each visit, disease activity was evaluated using the Birmingham Vasculitis Activity Score (BVAS) (12). Routine laboratory analysis included complete blood count, measurements of ESR, serum urea, creatinin, C-reactive protein (CRP), urinary sediment, and analysis of

24-h urinary protein. ANCA testing was performed locally at the time of diagnosis, during follow-up, and if relapse occurred. ANCA testing by IIF at the time of switch to azathioprine was performed centrally at the UMCG.

Remission was defined as a BVAS score of 0 and low stable CRP (< 10 mg/dl) (13). Relapse was defined as recurrence or the first appearance of one or more BVAS items attributable to active vasculitis (14).

The primary endpoint was relapse-free survival, defined as the time from remission to first relapse, at 4 years post-diagnosis. Secondary outcomes were the cumulative dosages of cyclophosphamide, prednisolone and azathioprine; cumulative organ damage; side effects due to study medication; and severity of relapses.

Statistical analysis

On the basis of our retrospective study, we anticipated that 50% of patients would be C-ANCA positive at the point of achieving stable remission (10). We calculated a predicted relapse rate of 80% at 4 years for patients with PR3-AAV who were C-ANCA positive at stable remission (10). The sample size was calculated based on the hypothesis that extended azathioprine maintenance therapy would reduce the 4year relapse risk by 30%, from 80% to 50%. Randomization of 90 C-ANCA- positive patients was required to achieve a power of 0.8 at a significance level of 0.05. Because we anticipated that 50% of enrolled patients would remain C-ANCA positive and thus be eligible for randomization, we aimed to include 180 patients with newly diagnosed PR3-AAV. Patients were randomized 1:1 to standard and extended azathioprine therapy. Closed envelopes with the randomized treatment duration were produced before inclusion of the first patient. Randomization was performed in blocks of four. Patients were stratified according to hospital, i.e., patients from the UMCG versus patients from other hospitals.

Analysis of the primary endpoint, the time from diagnosis until first relapse of disease, was based on the time to loss of follow-up, time to study end or time to 1 October 2014.

All analyses were performed with GraphPad Prism version 5.04. Groups were compared using Student's t-test or the χ^2 test. For comparison of non-parametric data, the Mann-Whitney-U test or Kruskal-Wallis test were used. Relapse-free survival curves were assessed by Kaplan-Meier estimates for survival distribution. Differences between groups in survival after 12 months of therapy were analyzed using log-rank tests. The primary analysis was performed on an intention-to-treat basis. Additionally, a per-protocol analysis, limited to patients who received treatment in full accordance with the study protocol, was conducted. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Between June 2003 and October 2011, 136 patients were enrolled in the study. Of these, five patients were excluded for various reasons (Figure 1). C-ANCA status was determined in 131 patients who achieved stable remission. Of these 131 patients, 86 patients (66%) were C-ANCA negative and therapy was switched to azathioprine with standard duration. Forty-five patients (34%) were C-ANCA positive at the time of stable remission and these patients were subsequently randomized. Of these 45 patients, 24 were randomized to standard duration of maintenance therapy and 21 patients were randomized to extended azathioprine maintenance therapy for 48 months after diagnosis.

Recruitment to trial was slower than anticipated, and C-ANCA positivity at stable remission (34%) was lower than expected. It was therefore concluded that the planned population of 90 C-ANCA- positive patients was not feasible within a reasonable time frame, and the decision was made in October 2011 to end enrolment prematurely, at which point 45 patients had been randomized.

Patient characteristics at baseline did not differ significantly between the three groups (Table 1). Most patients were diagnosed with GPA. Patients who were C-ANCA negative

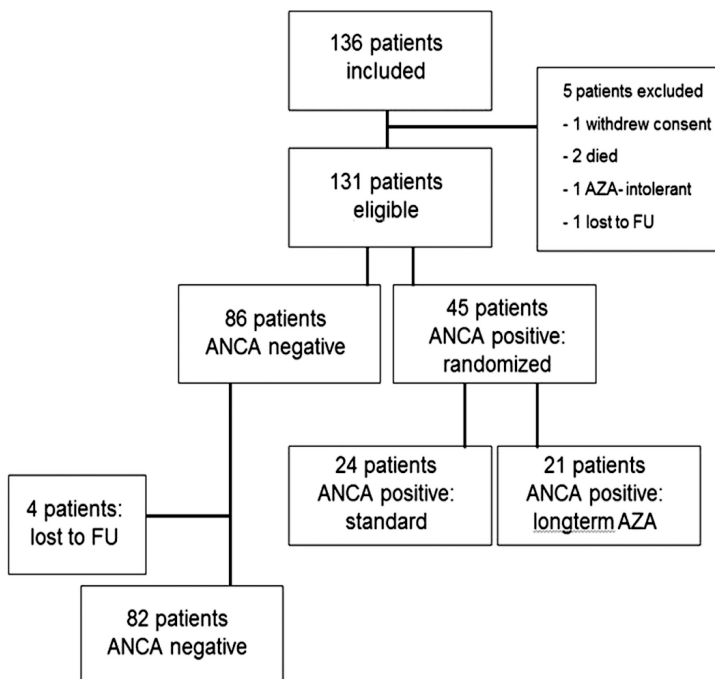


Figure 1 Flowchart of enrolment and randomization.

Table 1 Patient characteristics at diagnosis and at time of remission.

	C-ANCA negative	C-ANCA positive AZA standard	C-ANCA positive AZA extended	p
N	82	24	21	
Age (year)	55 (21-78)	53 (18-82)	56 (26-80)	0.36
Sex (men), n (%)	76 (62)	67 (16)	57 (12)	0.19
Diagnosis, n	78/2/4	23/0/1	19/0/2	
GPA/MPA/RL*				
Organ involvement:				
Renal, n (%)	62 (76)	16 (70)	16 (80)	0.49
Pulmonary, n (%)	45 (55)	16 (70)	13 (65)	0.66
ENT#, n (%)	62 (76)	20 (87)	11 (55)	0.12
BVAS	20 (8-33)	18 (8-33)	20 (9-39)	0.24
CRP (mg/l)	127 (2-350)	104 (2-286)	98 (1-347)	0.25
Creatinine at diagnosis (μ mol/l)	199 (50-1008)	144 (57-572)	155 (65-799)	0.40
Methylprednisolone, n (%)	28 (34)	4 (17)	6 (29)	0.26
RRT**, n (%)	8 (10)	0	1 (5)	0.06
PPh##, n (%)	22 (27)	2 (8)	2 (10)	0.24
Time to remission months	4.8 (1.8-8.7)	4.4 (2.5-7.5)	4.4 (2.5-8.9)	0.08
Creatinine at remission (μ mol/l)	130 (62-524)	109 (40-219)	102 (64-165)	0.47
Cyclophosphamide cumulative (gram), mean (SD)	17.7 (7.0)	14.7 (9.2)	13.2 (6.0)	0.10
Prednisolone cumulative (gram), mean (SD)	5.6 (1.9)	5.8 (2.0)	7.8 (3.5)	0.25
Treated per protocol, n (%)	67 (82)	22 (92)	17 (81)	0.48
Follow-up (months)	46.3 (25.8-52.9)	45.6 (24- 48.2)	45.2 (22-48.7)	0.37

Values are means and range unless indicated otherwise

* GPA/MPA/RL= granulomatosis with poly-angiitis/microscopic poly-angiitis/renal limited vasculitis.

#ENT = Ear, nose, throat

**RRT = Renal replacement therapy

##PPh= plasmapheresis

at the point of achieving stable remission were more likely to have renal insufficiency and require renal replacement therapy ($P=0.06$). There were no significant differences in the requirement for additional treatment with methylprednisolone or plasmapheresis. Cumulative cyclophosphamide and prednisolone dosages did not differ between the three groups. The mean time to stable remission was 4.6 months and was similar between the three groups. As expected, subsequent cumulative azathioprine dosages and durations were significantly higher in patients treated with extended azathioprine maintenance compared with patients given standard azathioprine maintenance therapy. In total, four patients were lost to follow-up during the study period.

Relapse-free survival

In total, 45 patients were C-ANCA positive at stable remission and were subsequently randomized, with 24 patients receiving standard-duration azathioprine maintenance therapy and 21 patients receiving extended azathioprine therapy. The primary endpoint was relapse-free survival 4 years after diagnosis.

Of the 24 patients on standard azathioprine therapy, 11 patients (46%) experienced a relapse within 4 years after diagnosis, compared with 5 of the 21 patients on extended azathioprine maintenance (24%). Cumulative estimated relapse-free survival in the standard group was 88 and 51%, at 2 and 4 years after diagnosis, respectively, compared with 78 and 72% in the extended treatment group {relative risk [RR] 0.65 [95% confidence interval (CI) 0.24-1.75]; $P=0.40$ } (Figure 2A). The severity of relapses, as measured by BVAS, CRP and organ involvement, did not differ between the two groups (Table 2).

Among the patients who were C-ANCA negative at switch ($n=82$), 33 patients (40%) experienced a relapse during follow-up within 4 years after diagnosis. For patients who received standard azathioprine maintenance, the cumulative estimated relapse-free survival at 2 and 4 years after diagnosis was 80 and 60%, respectively. Relapse risk, and the severity of relapses, did not differ significantly between the other two groups (Figure 2B and Table 2).

There was also no significant difference in relapse-free survival between all patients on standard azathioprine ($n=106$) compared with patients treated with extended azathioprine maintenance therapy ($n=21$; $P=0.94$) (supp mat, Figure S3A). Patients with PR3-AAV who were C-ANCA positive ($n=45$) and patients who were C-ANCA negative ($n=86$) at the time of remission did not differ significantly in terms of relapse rate ($P=0.62$) (supp mat, Figure S3B). C-ANCA positivity at switch was not significantly associated with the occurrence of relapse.

Per-protocol analysis

The per-protocol population excluded two patients in the C-ANCA- positive group randomized to standard therapy and four patients in the C-ANCA- positive group randomized to

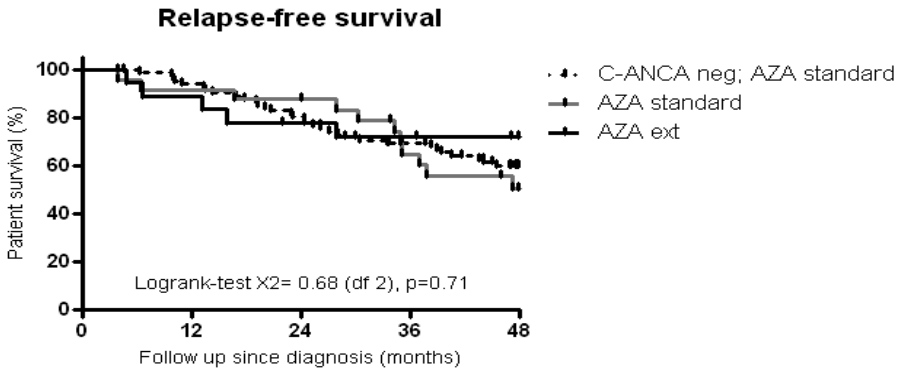


Figure 2A Relapse-free survival in C-ANCA positive patients randomized to standard and extended therapy.

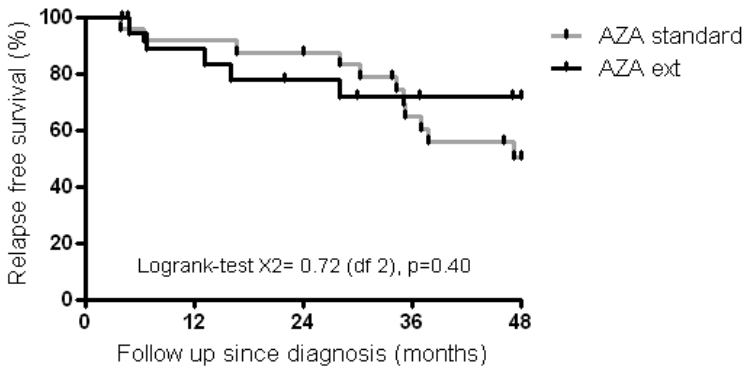


Figure 2B Relapse-free survival in C-ANCA negative patients at switch and C-ANCA positive patients randomized to standard and extended therapy.

extended azathioprine maintenance therapy. Azathioprine intolerance led to withdrawal of the study drug in four patients (three patients randomized to standard azathioprine and one patient randomized to extended azathioprine).

In the per-protocol analysis, relapse-free survival again did not differ significantly between C-ANCA- positive patients randomized to standard (n= 22) or extended azathioprine maintenance (n= 17) (P= 0.83). In the standard group, cumulative estimated relapse-free survival was 86 and 51%, at 2 and 4 years after diagnosis, respectively, compared to 71 and 63% in the extended group (RR 0.89; (95% CI 0.31-2.57); P= 0.83).

Table 2 Relapse characteristics.

	C-ANCA negative	C-ANCA positive AZA standard	C-ANCA positive AZA extended	p
Relapse, n (%)	33 (40)	11 (46)	5 (25)	0.28
Multiple relapses, n	4	2	2	
BVAS	12 (2-26)	14 (4-27))	9 (2-28)	0.30
CRP (mg/l)	46 (1-182)	70 (6-287)	95 (1-324)	0.62
Organ involvement:				
Renal, n (%)	15 (45)	8 (73)	2 (40)	0.26
Pulmonary, n (%)	5 (15)	3 (27)	1 (20)	0.66
ENT#, n (%)	15 (45)	7 (63)	1 (20)	0.26

Values are means and range unless indicated otherwise

#ENT = Ear, nose, throat

Death and adverse events

Eight patients died during the study. No deaths were directly attributable to study medication. Six of the patients who died were C-ANCA negative at remission and two were C-ANCA positive (both were randomized to extended azathioprine therapy). The causes of death were malignancy (n=4), infection (n=1), pulmonary fibrosis (n=1) and unknown (n=2). Survival was not significantly different between the three patient groups (P= 0.86).

The number of reported adverse events was not significantly different between the three groups (Table 3). In 24 patients in the C-ANCA- positive group treated with standard azathioprine, 27 adverse events were reported, compared with 19 adverse events in 21 C-ANCA positive patients treated with extended azathioprine (P=0.30).

Five severe infections were reported in both C-ANCA positive groups. Viral infective episodes were reported separately but were also not significantly different (P=0.67). In 13 C-ANCA negative patients, and in 3 patients in both the C-ANCA- positive groups, significant leukopenia led to a temporary dose reduction or withdrawal of azathioprine (P=0.91). Malignancy occurred in five patients in the C-ANCA- negative group (one bladder, two skin, two gastrointestinal), one patient in the C-ANCA- positive group treated with standard azathioprine therapy (breast cancer), and one patient in the extended azathioprine group (cholangiocarcinoma) (P= 0.92).

DISCUSSION

In this prospective, randomized study, we did not find a significant difference in relapse rate between standard-duration or extended-duration azathioprine maintenance therapy

Table 3 Adverse events.

	C-ANCA negative N (82)	C-ANCA positive AZA standard N (24)	C-ANCA positive AZA extended N (21)	p
Infection	10	5	5	0.32
CMV/HSV/HZV/Candida*	1/2/4/2	1/0/1/0	0/0/1/0	0.67
Diabetes Mellitus	8	3	3	0.81
Leucopenia	13	3	3	0.91
Thrombopenia	2	1	0	0.65
Cutaneous eruption	3	1	0	0.66
Eye involvement	3	1	0	0.66
ENT events#	0	1	0	0.12
Venous thrombosis	6	0	1	0.38
Gastrointestinal events	5	3	3	0.37
Liver toxicity	6	1	0	0.40
Polyneuropathy	1	0	0	0.76
Myopathy	1	0	1	0.40
Amaurosis fugax	1	0	0	0.76
Fractures	0	1	1	0.15
Non-STEMI	0	1	0	0.16
Pulmonary hypertension	1	0	0	0.76
Malignancy	5	1	1	0.92
Azathioprine intolerance	10	3	2	0.94
Death due to study drug	0	0	0	
Any adverse event	76	27	19	0.30

*CMV/HSV/HZV = cytomegalovirus/herpes simplex virus/herpes zoster virus

#ENT = Ear, nose, throat

in patients with PR3-AAV who were C-ANCA positive at the time of switch. A non-significant hazard ratio of 0.65 (95% CI 0.24-1.75; $P=0.40$) with extended versus standard therapy was observed after 4 years of follow-up. Moreover, the severity of relapse did not differ between treatment groups. Analysis of relapse in the patients who were treated as per protocol did not change these findings. Furthermore, we were not able to confirm our previous finding that the relapse rate is increased in patients who were persistently C-ANCA positive.

A major limitation of this study was its premature termination, which meant that the trial was seriously underpowered. A posthoc power calculation showed that the study had only a 23% power to detect a significant between-group difference in the primary endpoint using a two-sided Fisher's Exact test. On the basis of the observed relapse rates, 89 patients

were required in each treatment arm to achieve 80% power, i.e. > 178 C-ANCA positive patients would have had to be randomized. Because 34% of patients were C-ANCA-positive at stable remission, at least 523 patients with PR3-AAV would have been required. Alternatively, the absolute difference in proportions would have had to be at least 0.38 to achieve 80% power, representing a 4-year relapse rate in the extended azathioprine maintenance group of < 8%. Because these patients were all PR3-ANCA positive patients, a well-known risk factor for relapse (8,9), we do not believe this was realistic. Although our data suggest an effect of extended azathioprine maintenance therapy on prevention of relapse this cannot be confirmed due to the lack of power. The ongoing REMAIN study, which is also studying long-term azathioprine maintenance therapy in AAV, may help answer this question.

At baseline, we found no differences in disease severity between treatment groups. However, compared with our previous retrospective cohort of C-ANCA- positive patients (10), patients in the current study were older and had less ENT involvement. There was no difference in induction therapy because patients in both studies were treated with oral cyclophosphamide. As both age and renal failure are known to influence cyclophosphamide pharmacokinetics, the observed difference in age between the studies might have contributed to the difference in relapse rates, as might other patient and disease characteristics.

However, the most obvious reason for the difference between our retrospective and prospective studies is the size of the study populations: this study is considerably larger. Furthermore, this study has the important additional methodological advantage of prospective observation.

Since the CYCAZAREM study, azathioprine has been the maintenance agent of choice in AAV (2). The Kidney Disease: Improving Global Outcomes guideline advises a minimum duration of 18 months for azathioprine maintenance therapy (15). However, no evidence is available for longer duration of maintenance therapy. Because most relapses occur during tapering and discontinuation of immunosuppressive drugs, which typically takes place between months 12 and 24 after diagnosis, prolonging maintenance therapy in patients at highest risk for relapse is an attractive concept. PR3-ANCA positivity and renal function are major predictive factors for relapse in patients with AAV (8,16). However, although prolonging azathioprine maintenance therapy according to these risk factors seems rational, this study does not support this strategy, and other comparative data are lacking. Recent studies suggest that maintenance regimens with alternative agents, particularly rituximab, may be more effective than azathioprine maintenance therapy. The recently published MAINRITSAN study showed that after induction of remission with intravenous cyclophosphamide, rituximab was more effective in preventing relapse prevention than azathioprine after 2 of follow-up (17). Studies are required to confirm this finding, and to establish whether this is also true after induction therapy with rituximab.

The RAVE and the RITUXVAS trials have showed that induction of remission with rituximab without maintenance immunosuppression offered equal potency to induction with cyclophosphamide and subsequent azathioprine maintenance up to 18 months (18,(19). Besides the fact that our study was underpowered, several other limitations should be acknowledged. Induction therapy comprised oral cyclophosphamide, so results should be interpreted cautiously for patients treated with intravenous cyclophosphamide. Previously, induction of remission with intravenous cyclophosphamide was found to be as effective as oral cyclophosphamide, and to be associated with fewer episodes of leukopenia, but it has also been associated with a higher subsequent relapse rate (20). In patients treated with intravenous cyclophosphamide, extended azathioprine maintenance might therefore be more effective than following induction therapy with oral cyclophosphamide. Finally, this study was not blinded. Because relapse is based on the BVAS, which includes several components that are relatively subjective, this could have introduced bias. However, in this study the severity of relapses did not differ between the treatment groups, making it less likely that the unblinded design had an important influence on the results.

The overall relapse rate of 37% in our study is compatible with relapse rates in published studies of maintenance therapy with similar follow-up periods (3, 4). Therefore, in the light of the study limitations, we conclude that extended azathioprine maintenance therapy beyond 18 months has, if any, no more than a limited effect on the prevention of relapses in patients with PR3-AAV at 4 years after diagnosis.

Finally, adverse events were equally divided between the groups and comparable with earlier studies of azathioprine maintenance therapy (3,4). Long-term azathioprine therapy in our population was not associated with additional toxicity or infections, although potentially azathioprine-related toxicity could occur or only be recognized after longer follow-up.

In conclusion, this prospective study did not show that positive C-ANCA at the point of stable remission after induction therapy with oral cyclophosphamide is associated with a significantly increased risk of relapse in patients with PR3-AAV. Thus, the findings do not justify adoption of maintenance azathioprine therapy in this patient group. Furthermore, on the basis of our results we recommend a standard duration of azathioprine maintenance therapy (1.5-2.0 mg/kg/day for 1 year and subsequent tapering) after induction of stable remission with oral cyclophosphamide in patients with PR3-AAV.

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