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Long term azathioprine maintenance therapy in ANCA-associated vasculitis: combined results of long-term follow-up data

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Abstract

Objective. We studied whether in ANCA-associated vasculitis patients, duration of AZA maintenance influenced relapse rate during long-term follow-up.

Methods. Three hundred and eighty newly diagnosed ANCA-associated vasculitis patients from six European multicentre studies treated with AZA maintenance were included; 58% were male, median age at diagnosis 59.4 years (interquartile range: 48.3–68.2 years); granulomatosis with polyangiitis, n = 236; microscopic polyangiitis, n = 132; or renal limited vasculitis, n = 12. Patients were grouped according to the duration of AZA maintenance after remission induction: $\leqslant$18 months, $\leqslant$24 months, $\leqslant$36 months, $\leqslant$48 months or $>$ 48 months. Primary outcome was relapse-free survival at 60 months.

Results. During follow-up, 84 first relapses occurred during AZA-maintenance therapy (1 relapse per 117 patient months) and 71 after withdrawal of AZA (1 relapse/113 months). During the first 12 months after withdrawal, 20 relapses occurred (1 relapse/119 months) and 29 relapses $>$12 months after withdrawal (1 relapse/186 months). Relapse-free survival at 60 months was 65.3% for patients receiving AZA maintenance $>$18 months after diagnosis *vs* 55% for those who discontinued maintenance $\leqslant$18 months (P = 0.11). Relapse-free survival was associated with induction therapy (i.v. *vs* oral) and ANCA specificity (PR3-ANCA *vs* MPO-ANCA/negative).

Conclusion. *Post hoc* analysis of combined trial data suggest that stopping AZA maintenance therapy does not lead to a significant increase in relapse rate and AZA maintenance for more than 18 months after diagnosis does not significantly influence relapse-free survival. ANCA specificity has more effect on relapse-free survival than duration of maintenance therapy and should be used to tailor therapy individually.

Key words: ANCA, PR3, granulomatosis with polyangiitis, vasculitis, azathioprine, maintenance, long-term follow-up, EUVAS, FVSG

CLINICAL SCIENCE

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Rheumatology key messages

- Extension of azathioprine maintenance therapy beyond 18 months seemed ineffective in preventing relapse in ANCA-associated vasculitis.
- Intravenous administration of cyclophosphamide, PR3-ANCA and higher serum creatinine are associated with relapse in ANCA-associated vasculitis.
- Duration and dose of glucocorticoids co-treatment in ANCA-associated vasculitis should receive further attention in future studies.

Introduction

Active ANCA-associated vasculitis (AAV) can be successfully treated with CYC or rituximab, combined with glucocorticoids. AAV is a chronic relapsing disease with substantial morbidity and mortality due to either the disease itself or the toxicity of long-term and repeated treatment [1–5]. Untreated, AAV is almost invariably fatal [6]. However, with the advent of immunosuppression, outcomes have improved considerably with 10-year survival reaching 60–90%. Disease remission is typically induced using CYC and glucocorticoids over 3–6 months, allowing remission rates of 80–90% [4, 7]. Once remission has been achieved, immunosuppressive regimens are converted to less toxic maintenance treatments such as AZA or MMF. However, disease relapses remain common, occurring in 50% of patients within 5 years [8]. Relapses are associated with accrual of organ damage and morbidity.

Randomized trials have compared various remission maintenance treatments including MTX, MMF and AZA [4, 5]. Although these studies have established AZA as the superior maintenance therapy and MTX in non-renal patients, the optimal duration of maintenance therapy is unknown. Current treatment guidelines recommend discontinuation of maintenance therapy after 18–24 months, since this was the typical maintenance treatment duration in previous clinical trials [4, 5, 7, 9]. Given this, it is striking that most relapses occur during or after withdrawal of maintenance therapy [10–12] consistent with the median disease-free survival of 21.8 (range 9.8–27) months after diagnosis [13–16]. It is therefore reasonable to postulate that relapse rates may be reduced by extending the duration of maintenance therapy.

However, in a prospective study of 146 patients with PR3-ANCA-associated vasculitis who remained ANCA positive at the time of remission, relapse rates were similar between those treated with AZA for the standard treatment duration (n = 23) and those receiving longer treatment duration (48 months, n = 21) [17, 18]. In the rituximab for induction-remission trial, the rituximab arm received no additional maintenance treatment at all but had the same outcomes on relapse rate at 18 months of follow-up compared with sequential CYC and AZA [19]. Both outcomes may thus raise questions about the influence on relapse rate and the overall efficacy of AZA 'maintenance'.

Using patient-level data from several landmark trials [4, 5, 7, 20–22] with extended follow-up from the European Vasculitis Study Group (EUVAS) and the French Vasculitis Study Group, we assessed the duration of maintenance therapy with AZA and its effect on relapses during long-term follow-up. In these trials, AZA was administrated during long-term follow-up for a period of 18–48 months, with follow-up until 60 months and longer, thus allowing evaluation of the effect of treatment duration on relapse rate.

Methods

We included long-term data from five EUVAS trials and one French Vasculitis Study Group trial [4, 5, 7, 10, 21, 22].

Long term follow-up data beyond the defined follow-up of the prospective studies were collected retrospectively by contacting the original investigators once to provide cumulative follow-up data after termination of the original studies.

This resulted in individual data from 759 AAV patients, enrolled between 1995 and January 2009 from 70 hospitals in 15 countries. The trials were conducted according to the Declaration of Helsinki and subsequent amendments and had received ethical board approval in each participating country; this study did not require additional approval or consent. All patients had newly diagnosed granulomatosis with polyangiitis (GPA), microscopic polyangiitis or renal limited vasculitis at trial entry, according to Chapel Hill Consensus Conference definitions.

Data collection and assessment

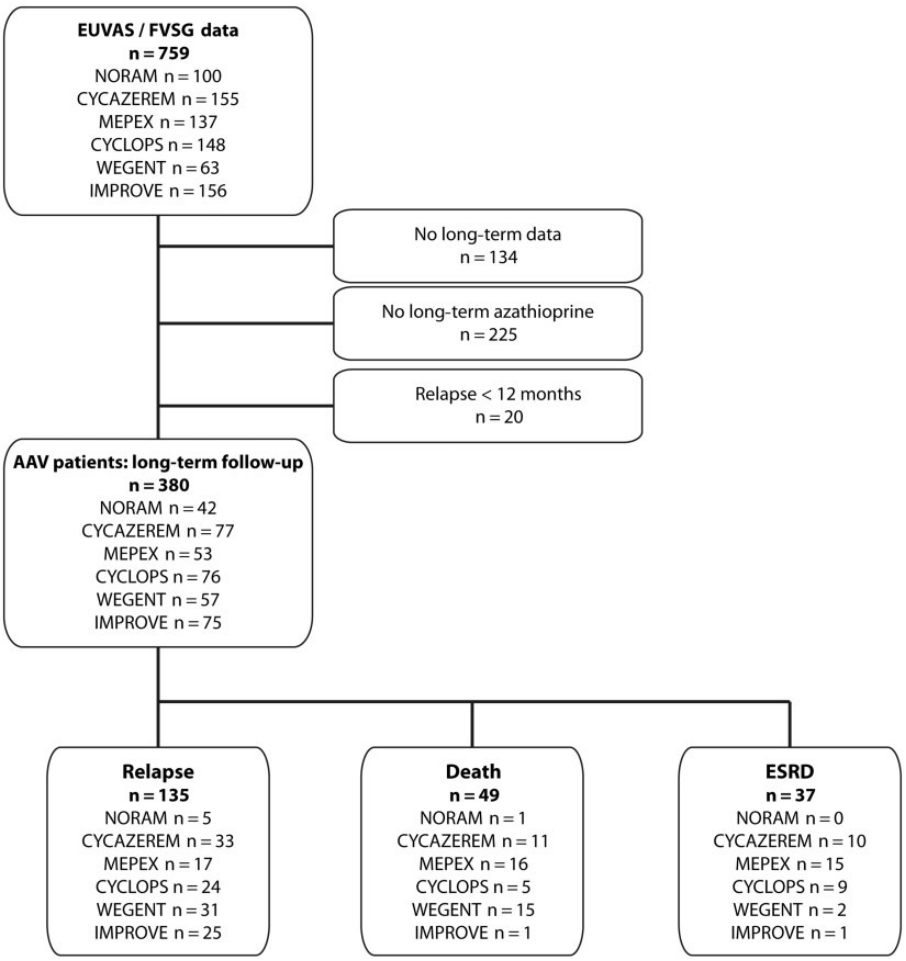
In order to assess the relationship between AZA maintenance duration and relapse risk, we excluded from the analysis all patients who did not receive AZA as remission maintenance ($n = 225$), those with <12 months follow-up data ($n = 134$) and those experiencing relapse during the first 12 months ($n = 20$) (Fig. 1). The analysis cohort ($n = 380$) was assigned to one of six bins based on the duration of AZA treatment: <12, 12–18, 19–24, 25–36, 37–48 and 49–60 months.

Since the patients in the NORAM trial received no AZA maintenance therapy after 12 months of induction therapy with CYC, these patients were considered as a separate group and analysed separately.

Statistical analysis

Summary data are presented as mean (SD) or median and interquartile range as appropriate. Between-group tests of proportions were carried out using the χ^2 test. For comparison of non-parametric data, the Mann–Whitney *U* test or Kruskall–Wallis test with *post hoc* test for >2 groups comparison was used. The primary outcome of our analysis was relapse-free survival and was assessed by Kaplan–Meier estimates for survival distribution. Survival estimates between groups were compared using the log-rank test. Univariate analysis was used to focus on the influence of discontinuation or continuation of AZA after 18, 24, 36, 48

Fig. 1 All ANCA-associated vasculitis patients included in the European and French vasculitis study groups' studies



AAV: ANCA-associated vasculitis; ESRD: end-stage renal disease; EUVAS: European Vasculitis Study Group; FVSG: French Vasculitis Study Group.

and 60 months on relapse risks. Multivariate analysis using the Cox proportional hazards models, with withdrawal of AZA as the time-dependent variable, was focused on differences between continuation of AZA, the period < 12 months after discontinuation of AZA and the period > 12 months after discontinuation of AZA. Other co-variates in the multivariable model were age at presentation, sex, diagnosis (GPA *vs* microscopic polyangiitis), route of CYC administration (i.v. *vs* oral), duration of induction therapy, serum creatinine at presentation and BVAS at diagnosis. For all comparisons, a two-sided $P < 0.05$ was considered statistically significant. Analyses were performed using SPSS Statistics v. 22 (IBM Corp., Armonk, NY, USA) and Prism v. 5.01 (GraphPad Software, La Jolla, CA, USA).

Results

Patients

Of all 759 AAV patients, eventually 380 patients were included in the analysis (Fig. 1). For these patients, baseline characteristics for each trial cohort are shown in Table 1. All main characteristics and outcomes of the original clinical studies are summarized in supplementary Table S1, available at *Rheumatology* Online. Trial cohorts differed obviously in outcome, but also in such characteristics as age, gender distribution and disease severity, as reflected in the baseline criteria (Table 1).

Overall, 221 (58%) patients were male. Median age at trial entry was 59.4 (48.3–68.2) years. Median serum creatinine was 142 (80–197) μmol/l and initial median BVAS was 19 (13–25). Two hundred and thirty-six (62%) patients had GPA, while 225 (59%) patients were anti-PR3 positive.

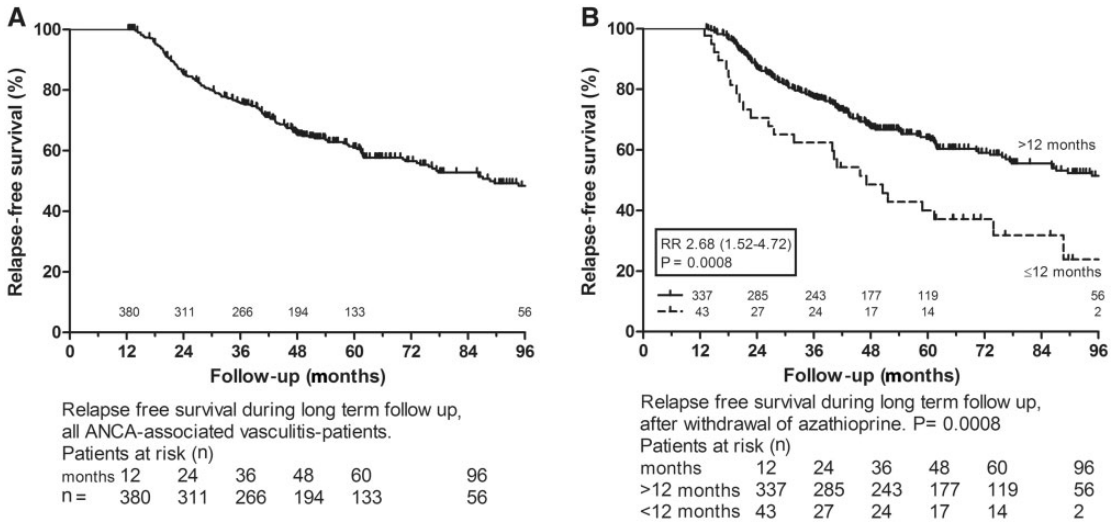
The protocol-defined duration of AZA therapy varied from <12 to 42 months and was left to the discretion of the physicians thereafter with the exception of IMPROVE, where maintenance was withdrawn after 42 months [4, 5, 7, 20–22]. Median time of follow-up was 65.4 months after diagnosis.

Table 1 Baseline characteristics of all included ANCA-associated vasculitis patients

n	cycaZArem 77	NORAM 42	MEPEX 53	CYCLOPS 76	WEGENT 56	IMPROVE 75
Sex, M/F	36/41	20/22	37/16	42/34	32/25	55/20
Age, median (range), years	56.8 (47.3–66.5)	53.5 (22–78)	64.8 (56.7–70.3)	60.7 (49.1–68.5)	59.3 (47.2–68.6)	61 (47.7–67.1)
GPA/MPA/RLV	50/27/0	40/2/0	25/28/0	28/36/12	43/14/0	50/25/0
PR3/MPO/neg	48/17/12	33/5/4	30/18/5	34/41/1	36/17/4	44/22/9
BVAS, median (range)	18 (10–24)	15 (42–149)	20 (15–26)	20 (15–23)	24 (20–29)	19 (7–25)
Serum creatinine, median (range)	146 (90–263)	84.5 (42–149)	724 (550–912)	162 (115–268)	15 (79–179)	177 (104–311)
Organ involvement, n (%)						
ENT	39 (51)	42 (91)	23 (53)	45 (59)	39 (70)	28 (37)
Pulmonary	44 (58)	24 (51)	18 (42)	45 (49)	44 (79)	36 (48)
Renal	71 (93)	15 (32)	43 (100)	75 (99)	45 (80)	42 (56)
Other	41 (53)	19 (41)	22 (51)	42 (55)	30 (54)	20 (27)

GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RLV: renal limited vasculitis.

Fig. 2 Relapse-free survival for all patients (A) and after withdrawal of AZA (B)



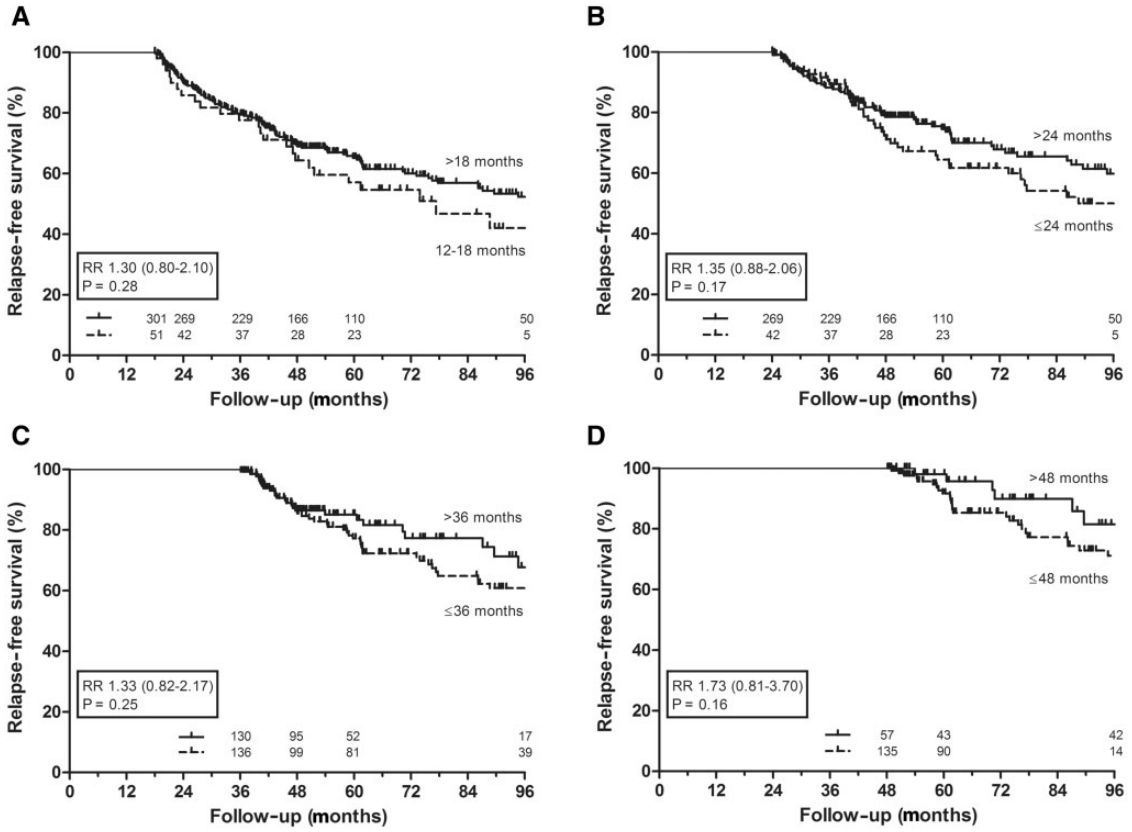
Relapse-free survival during long-term follow-up (**A**) after withdrawal of AZA and (**B**) for all ANCA-associated vasculitis patients.

Relapses

During follow-up, 155 patients (40.8%) had a first relapse; 84 first relapses occurred during AZA maintenance therapy (1 relapse per 117 patient months) and 71 after discontinuation of AZA. Of these 71 relapses, 49 occurred within 60 months after diagnosis (1 relapse/113 months) and 22 thereafter. During the first 12 months after stopping AZA, 20 relapses occurred (1 relapse/119 months). Twenty-nine relapses occurred between 12 and 60 months after discontinuation of AZA (1 relapse/186 months) (Fig. 2A and B). Relapse-free survival at 60 months after diagnosis was 65.3% for patients receiving AZA maintenance >18 months after diagnosis *vs* 55.0% for those who stopped maintenance ⩽18 months (P = 0.11) (Fig. 3A). At all later time points of discontinuing AZA maintenance therapy, comparing duration >24 and ⩽24, >36 and ⩽36 and >48 and ⩽48 months, a numerically small and not statistically significant increase in relapses was found (Fig. 3B–D). Relapse-free survival was lower in patients who were treated with intravenous CYC compared with oral treatment (P = 0.042) and lower in patients with PR3-ANCA compared with MPO-ANCA (P = 0.011).

In a multivariate Cox proportional hazard model, relapse risk was associated with successful discontinuation (without relapse) of AZA during a period of >12 months [P = 0.027, hazard ratio (HR) = 0.57, 95% CI: 0.35, 0.94]. Thus, when no relapse occurred shortly, i.e. ⩽12 months, after

FIG. 3 Relapse-free survival curves for patients at risk on withdrawal after 18–48 months after diagnosis



Relapse-free survival maintenance (**A**) >18 *vs* 12–18 months, (**B**) >24 *vs* ⩽24 months, (**C**) >36 *vs* ⩽36 months, and (**D**) >48 *vs* ⩽48 months.

withdrawal of AZA, the relapse risk seemed to be decreased during long-term follow-up. Increased relapse risk was associated with i.v. *vs* oral CYC route (HR = 1.20, 95% CI: 1.04, 1.43; P = 0.023), PR3-ANCA (HR = 1.32, 95% CI: 1.10, 1.57, P = 0.002) and creatinine at diagnosis (HR = 0.99, 95% CI: 0.998, 1.000; P = 0.032) (Table 2).

Patients in the NORAM trial, who did not receive maintenance beyond 12 months after diagnosis, had a reduced 60 months actuarial relapse-free survival (39.9% *vs* 65.3%; P = 0.001) (Fig. 2B).

TABLE 2 Multivariate Cox proportional hazard analysis on risk of relapse during long-term follow-up

	HR (95% CI)	P-value
CYC i.v. *vs* oral	1.206 (1.015, 1.432)	0.023
PR3 *vs* other/none	1.316 (1.100, 1.574)	0.002
Creatinine (diagnosis)	0.999 (0.998, 1.000)	0.032
AZA use (yes/no)	1.286 (0.870, 1.901)	0.212
Stopped <12 months	1.183 (0.739, 1.895)[a]	0.227
Stopped >12 months	0.570 (0.347, 0.937)[a]	0.027

[a]As compared with current use. HR: hazard ratio.

Secondary outcomes: mortality and end-stage renal disease

Of the selected patients who survived the first year without experiencing any relapse, 94 (13%) died during long-term follow-up, resulting in a survival at 12 months after diagnosis of 98%, of 93% at 60 months and 82% at 10 years after diagnosis. We did not find a difference in mortality between the groups with different AZA duration, that is, <12, 12–18, 19–24, 25–36, 36–48 and 49–60 months.

Causes of death were mainly cardiovascular and infectious (supplementary Table S2, available at *Rheumatology* Online). Thirty-seven patients (10%) reached end-stage renal disease (for distribution, see also Fig. 1).

Adverse events

Serious adverse events that could have been related to immunosuppressive treatment were recorded during long-term follow-up. As depicted in Table 3, infection was the most documented adverse event but no difference in occurrence was found between groups (P = 0.07). Also, there was no difference for cardiovascular events

Table 3 Occurrence of at least one period of adverse event potentially related to drug regimen

NORAM	> 6 months	6–18 months	19–24 months	25–36 months	37–48 months	49–60 months	P-value
Number of patients, n	44	46	78	58	74	81	
Infection, n (%)	2 (5)	23 (34)	19 (34)	19 (33)	27 (36)	10 (23)	0.07
CHD, n (%)	2 (5)	3 (7)	7 (9)	9 (16)	7 (9)	8 (10)	0.64
Malignancy, n (%)	4 (9)	—	7 (9)	6 (10)	8 (11)	9 (11)	0.24
Diabetes Mellitus, n (%)	2 (5)	5 (11)	7 (9)	6 (10)	11 (15)	6 (7)	0.63
Bone disorders, n (%)	2 (5)	4 (9)	5 (6)	5 (9)	4 (5)	3 (4)	0.73
Thrombotic event, n (%)	1 (2)	2 (4)	2 (3)	6 (10)	6 (8)	7 (9)	0.35

[including cardiac events, stroke and revascularization procedure (P = 0.64), malignancy (P = 0.24), diabetes mellitus (P = 0.63), thrombotic events (P = 0.35) or bone disorders (P = 0.73)].

Discussion

We studied the relationship between duration of maintenance therapy and occurrence of relapses in an international cohort of 380 trial participants with AAV who were followed during and after termination of long-term maintenance therapy. We identified an increased relapse risk with AZA treatment duration <12 months after diagnosis. Although for all analysed time points of discontinuing AZA maintenance therapy beyond 18 months there seems to be a numerical advantage for longer duration of maintenance and an inverse relationship between AZA treatment duration and the risk of relapse (Fig. 3A–D), this difference did not reach statistical significance.

A power calculation on the basis of the observed relapse rate of 50% at 60 months and a relapse-free survival difference of 8–10% (HR = 1.2–1.3) showed that, to reach significance (P = 0.05), 360 or 510 patients would have been required in each treatment arm to achieve 80% or 90% power, respectively. We confirmed the previously described association between intravenous route CYC, anti-PR3 ANCA and higher serum creatinine at diagnosis with increased risk of relapse [7–9].

Ever since its introduction by Fauci *et al.* in 1983, induction treatment followed by remission maintenance has be the norm for the treatment of AAV [23]. Slot and colleagues [17] demonstrated ongoing relapse risk with follow-up of 42 months, particularly in patients who were ANCA-positive at remission, providing a rationale for extended maintenance treatment duration. However, the optimum duration of maintenance therapy remains uncertain, partly due to the fact that follow-up in clinical trials has often been <2 years [4, 9].

Moreover, in a prospective study of 126 patients with PR3-ANCA-associated vasculitis, the association of persistent ANCA positivity and higher relapse risk was not confirmed and longer AZA use was not associated with decrease in relapse rate [19]. These findings may suggest, in line with our present finding, that the long-term effect is perhaps more related to the intensity of induction treatment than due to maintenance therapy. The results of a multicentre remission of maintenance study comparing short- and long-term courses of AZA maintenance therapy (REMAIN) may contribute to this debate [24].

In contrast, the IMPROVE trial showed that maintenance therapy for >20 months with MMF was less effective in prevention of relapse compared with AZA [5]. Outcome in relapse rate was adjusted for a diversity of pre-specified factors that could have influenced relapse-risk such diagnostic subtype, route of CYC administration and baseline serum creatinine level: by multivariate analysis, the HR for relapse associated with MMF use was 1.80 (95% CI: 1.10, 2.93; P = 0.02). This demonstrates both the importance of maintenance therapy in preventing relapse, and the fact that this may depend on the choice of agent [5]. Comparing AZA to MTX as maintenance agent did not demonstrate differences in relapse rate [21]. Recently, rituximab maintenance therapy following CYC induction therapy was shown to be superior in reducing relapse rate (P < 0.0001) compared with AZA in the MAINRITSAN trial [25]. Also, the RITAZEREM trial, which is currently still recruiting patients, will test whether rituximab is superior to AZA in the prevention of exacerbations in AAV patients with relapsing disease [26].

Given this aforementioned variation in relapse rates observed with different treatments and durations, uncertainty remains over the optimal duration of maintenance. Further, the relative contribution of remission maintenance regimen and duration compared with other known predictors of relapse such as ANCA subtype, baseline renal function and induction regimen remains not fully elucidated since, for instance, the recently published data of the long-term follow-up of the CYCAZEREM suggests a trend to more relapses in the shorter CYC exposure group. Also in this present study, relapse rate was not different in any of the AZA duration groups, while baseline characteristics and treatment were different.

Another important issue of debate is the role of long-term use of low-dose steroids in the prevention of relapse, which has not been adequately evaluated to date. Since some claim that steroids improve disease control and in most trial protocols the use of steroids often is left to the discretion of the treating physician, this situation makes it harder to make a statement on the other immunosuppressive agents. However, we also know that there is

considerable difference in belief in the use of steroids between doctors, centres and countries, and there is an urgency to study the effects on steroids in the near future.

Next to doubts about necessity of maintenance, longer duration of immunosuppressive therapy could be related to an increase of, for instance, infectious or cardiovascular adverse events in those patients who are treated for >18 months [3, 9]. In our study, these adverse effects were equally divided and not statistically different between the groups on various durations of maintenance. Causes of death mainly were cardiovascular causes and infection; whether these causes could have been related to either disease or treatment is unclear since other covariates like duration and dosage of induction therapy could have contributed. Due to the nature of the original trials, mean baseline serum creatinine was unequally divided between these groups, so conclusions cannot be drawn from our findings on end-stage renal disease.

The results of our study must be viewed in terms of their limitations. Although we were given the opportunity to compare long-term follow-up data of six landmark studies, these were largely extended follow-up data that were reported and collected retrospectively beyond the scope and defined follow-up of the original studies. Data analysis was performed only on a selection of patients from heterogeneous trial protocols, in which patient characteristics, induction treatment as well as disease severity differed. This could have led to difference in the cohorts of patients who were included in our analysis and in outcome since the analyses are only performed on patients who survived the first year after diagnosis without any relapse during this year. Unfortunately, we were also only able to compare long-term outcomes by using clinical information collected at baseline; we are aware that the course of disease or the clinical situation could have influenced physicians' decisions on AZA duration. These follow-up courses were not protocol determined and the reasons for continuing or changing management are not documented: this could have introduced 'confounding by indication'. Also, the long-term follow-up outside trial protocol could have led to attrition in the follow-up: maybe one tends to follow patients with extensive disease for a longer period. Furthermore, data collection may have not been optimal and for instance adverse events may have been under-reported.

Another major drawback is that we are not informed about dose and duration of glucocorticoids co-treatment during follow-up. In a large meta-analysis focused on the use of glucocorticoid, Walsh *et al*. concluded that earlier withdrawal of corticosteroids (discontinuation < 12 months) was associated with increased relapse [27]; this may have obscured our findings and therefore may be considered an important limitation.

The comparison of heterogeneous trials that included different patient populations within the whole spectrum of AAV may lead to inconsistent findings. Unfortunately, due to the limited numbers, analyses of subgroups like for instance populations with different induction schemes, were not feasible. However, since this is also the population encountered in daily clinical practice, we think our findings can be applicable and are likely generalizable to patients with AAV in daily clinic.

To summarize, on the basis of our findings, we think there is no clear evidence that extension of maintenance therapy with AZA maintenance therapy beyond 18 months after diagnosis in general is effective in relapse prevention. We do realize that this finding may not be applicable to certain group of patients who may have higher risk of relapse or other specific characteristics.

Intravenous administration of CYC, PR3-ANCA and higher serum creatinine at diagnosis are significantly associated with relapse. Mortality was equally divided between the groups in our study and independent of duration of maintenance therapy, as were side effects that are known to be related to the long-term treatment. Further research will hopefully elucidate the need for and benefits of maintenance therapy in ANCA-associated vasculitis in all the aspects of disease: the data of a large multicentre maintenance of remission study comparing short- and long-term courses of AZA maintenance therapy are not yet published but, hopefully, the results of this large study will enable clinicians in daily practice to decide what maintenance agent to choose and for how long [24].

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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