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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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Submitted

ABSTRACT

Objectives

We studied whether in ANCA-associated vasculitis (AAV) patients, the duration of azathioprine maintenance therapy following cyclophosphamide induction therapy influenced relapse rate during long term follow up.

Methods

We included 380 newly diagnosed AAV-patients from six European multicenter studies with available long term follow up data and treated with azathioprine maintenance after successful remission induction with cyclophosphamide and high dose corticosteroids. The trials differed in inclusion criteria (disease severity) and in the duration of maintenance therapy. Patients were combined from all six studies and grouped according to the duration of azathioprine maintenance after remission induction: ≤18 months / ≤ 24 months /≤36 months /≤ 48 months / > 48 months. Primary outcome was relapse free survival at 60 months.

Results

380 patients, 58% male, median age at diagnosis 59.4 years (IQR 48.3-68.2) with GPA (n=236), MPA (n=132) or RLV (n=12) were included. Most patients, (n= 225, 59%) were anti-PR3 positive, 120 (32%) anti-MPO-positive and 35 (9%) ANCA negative. During follow up, 155 patients (40.8%) had a first relapse; 84 first relapses occurred during azathioprine-maintenance therapy (1 relapse per 117 patient months) and 71 after stopping azathioprine of which 49 occurred within 60 months after diagnosis (1 relapse/113 months) and 22 thereafter. During the first 12 months after stopping azathioprine, 20 relapses occurred (1 relapse/119 months). Twenty-nine relapses occurred between 12-60 months after discontinuation of azathioprine (1 relapse/186 months). Relapse free survival at 60 months after diagnosis was 65.3% for patients receiving azathioprine maintenance >18 months after diagnosis versus 55% for those who stopped maintenance ≤18 months (p 0.11). Relapse-free survival was furthermore associated with type of induction therapy (intravenous versus oral) and ANCA-specificity (PR3-ANCA versus MPO-ANCA/negative). Forty-nine patients (13%) died during long term follow up, resulting in a survival of 98%, 93% and 84% at 24 months, 60 months and 10 years after diagnosis respectively. Thirty-seven (10%) of all AAV-patients reached ESRD with a median follow up of 61.5 years.

Conclusions

Post-hoc analysis of combined trial data suggest that stopping azathioprine maintenance therapy does not lead to a significant increase in relapse rate and that azathioprine 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 the duration of maintenance therapy and should be used to tailor therapy individually.

INTRODUCTION

Active anti-neutrophil cytoplasm auto-antibody (ANCA) associated vasculitis (AAV) can be successfully treated with cyclophosphamide or rituximab, combined with glucocorticoids. AAV is a chronic relapsing disease with substantial morbidity and mortality due to either 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 cyclophosphamide and glucocorticoids over 3 to 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 azathioprine or mycophenolate mofetil. 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 methotrexate, mycophenolate mofetil and azathioprine (4,5). Although these studies have established azathioprine as the superior maintenance therapy and methotrexate in non-renal patients, the optimal duration of maintenance therapy however 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 (4-6,9,10). Given this, it is striking that most relapses occur during or after withdrawal of maintenance therapy (11-13), consistent with the median disease-free survival of 21.8 (range 9.8-27) months after diagnosis (14-17). 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,, relapses rates were similar between those treated with azathioprine for the standard treatment duration (n=23) versus those receiving longer treatment duration (48 months, n=21) (18,19). In the rituximab for induction-remission trail (RAVE), 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 cyclophosphamide and azathioprine (20). Both outcomes may thus raise questions about the influence on relapse rate and the overall efficacy of azathioprine 'maintenance'.
Using patient-level data from several landmark trials (4,5,7,10,21,22) with extended follow-up from the European (EUVAS) and French Vasculitis Study Groups (FVSG), we assessed the duration of maintenance therapy with azathioprine and its effect on relapses during long term follow up. In these trails, azathioprine 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 FVSG trial (4,5,7,10,21,22). 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 Helsinki declaration and subsequent amendments and had received ethical board approval in each participating country. All patients had newly diagnosed GPA, MPA 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 azathioprine maintenance duration and relapse risk, we excluded from the analysis all patients who did not receive azathioprine as remission maintenance (n=225), those with less than 12 months follow-up data (n=134), and those experiencing relapse during the first 12 months (n=20) (Figure 1). The analysis cohort (n=380) were assigned to one of 6 bins based on the duration of azathioprine

Table 1 Main characteristics of original trials included

	Inclusion	Induction	Maintenance
CYCAZEREM Jayne et al, 2003 N=144	Newly diagnosed WG/ MPA/RLGN seCreat < 500 umol/l.	Cyc oral 2 mg/kg/day Pred 1 mg/kg/day	Cyc 1.5 mg/kg/day + pred N= 73 AZA 2 mg/kg/day + pred N=71
NORAM De Groot et al, 2005 N=100	Newly diagnosed AASV seCreat < 150 umol/l Without critical organ manifestations	Cyc oral 2 mg/kg N= 46 or MTX oral, 20-25 mg/ wk N = 49 + Pred 1 mg/kg/day	Cyc 1.5 mg/kg/day + pred N = 44 MTX oral, 20-25 mg/ wk N = 47

treatment: < 12 months, 12-18 months, 19-24, 25-36, 37-48 and 49-60 months.
Since the patients in the NORAM-trial received no azathioprine maintenance therapy after 12 months of induction therapy with cyclophosphamide, these patients were considered as a separate group and analyzed 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 chi-square test. For comparison of non-parametric data, the Mann-Whitney U test or Kruskall Wallis-test with post-test for > two group 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

Duration	Relapse	AE's
Treatment and FU 18 months	CYC: N=10, 13.7%	CYC: N=7, 10%
	AZA: N=11, 15.5%	AZA: N=8, 11%
	P 0.65	P 0.94
		Death N=1.
Treatment 12 months	(major)	N= 51 (83 episodes)
	CYC:	CYC:
FU 18 months	N=9	Mild/moderate: 39 episodes
	20%	Severe to life threatening: 6 episodes
	MTX:	MTX:
	N=17	Mild/moderate: 29 episodes
	36%	Severe to life threatening: 9 episodes
	P 0.11	Death CYC N=2 (4%) MTX N=2 (4%)

Table 1 Continued

	Inclusion	Induction	Maintenance
MEPEX Jayne et al, 2007 N=137	Newly diagnosed AAV confirmed by renal biopsy and seCreat > 500 umol/l.	Plasma exchange N= 70 or Methylprednisolone 3000 mg N=67 and CYC oral 2.5 mg/kg/day +Pred 1 mg/kg/day	AZA 2 mg/kg/day after month 6
CYCLOPS De Groot et al, 2009. N=149	Newly diagnosed AAV with renal involvement	CYC i.v 15 mg/kg every 2-3 wks N=76 or CYC oral 2 mg/kg/day N=73 Both groups + Pred 1 mg/kg	AZA 2 mg/kg/day from 3 months after remission until month 18.
WEGENT Pagnoux et al, 2008. N=126	WG/MPA	CYC i.v 0.6 mg/0.6 x m2 first two weeks, thereafter 0.7 mg/m2 every three weeks. Pred 1 mg/kg/day	AZA 2.0 mg/kg/day N=63 MTX 0.3 mg/kg/wk N=63
IMPROVE Hiemstra et al, 2010 N=156	Newly diagnosed AAV (WG/MPA)	CYC 1.5-2 mg/kg/day + Pred 1 mg/kg/day	AZA 2 mg/kg/day N=80 MMF 2000 mg/day N=76

Duration	Relapse	AE's
Treatment and FU 12 months	N=2 (not mentioned in original article)	N=122 (244 episodes) - N=67 severe to life-threatening -PLEX N= 35 (50%) - Methyl N=32 (48%) P 0.80 Death PLEX N=19 (27%) Methyl N=16 (24%) P 0.68
Treatment and FU 18 months (0.25-18 months)	All patients N=19 (14.5%) CYC i.v N=13 (17%) CYC oral N=6 (8%) HR 2.01.	N= 114 (228 episodes) - N=85 mild to moderate - N=29 severe to life-threatening Death CYC i.v N=5 (7%) CYC oral N=9 (12%) P 0.79.
Treatment 15 months FU 29+/- 13 months	AZA: N=23, 37% MTX: N=21, 33% P 0.71	AZA: N=29, 46% MTX: N=35, 56% P 0.29. Death N=1 (MTX)
Treatment 39 months (0.66-53.6) FU 42 months	AZA: N=30, 37% MMF: N=42, 55% P 0.03	AZA: N=13, 16% MMF N=8, 7.5% P 0.12 Death N=2 (1 AZA, 1 MTX)

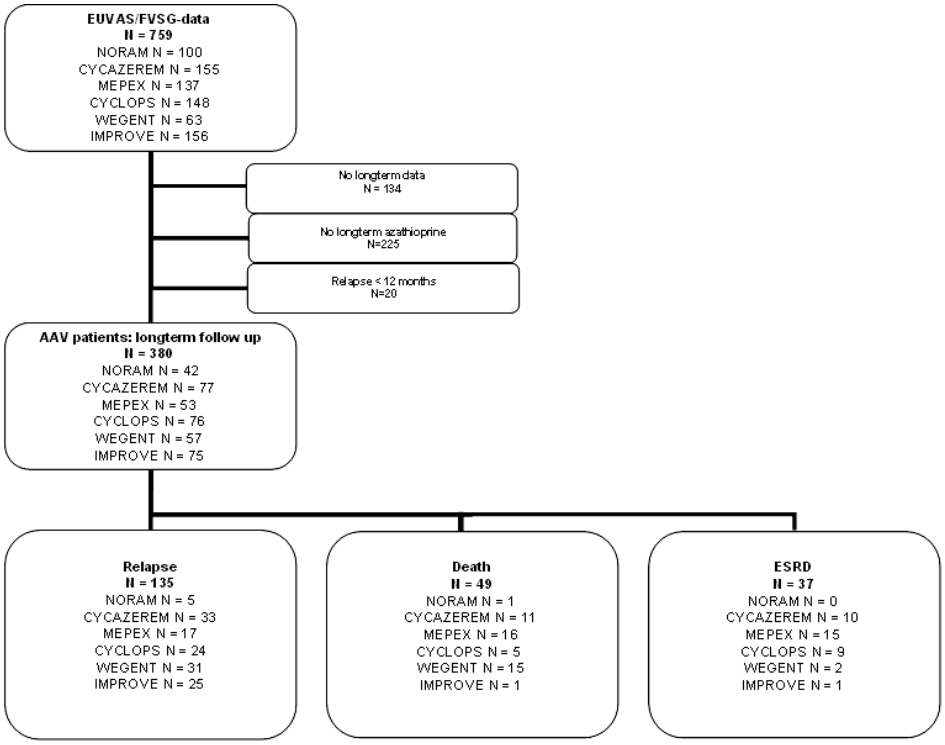

Figure 1A Flowchart on included studies and number of excluded data.

	Originally included	Original/ longterm Aza	Relapse < 12 mths	Included in analysis	Mean FU (mths)
NORAM	100	-	-	46	61,8
CYCAZEREM	155	71/ 77	4*	77	78,2
MEPEX	137	54	1**	53	44,3
CYCLOPS	149	76	2	76	46,4
WEGENT	159	63	6	57	97,8
IMPROVE	156	80	5	75	40,2

Figure 1B Flowchart on included studies and number of excluded data.

* 4 early relapses happened in patients who were not on long term azathioprine

** 2 relapses happened in patients who were not on long term azathioprine

azathioprine after 18, 24, 36, 48 and 60 months on relapse risks. Multivariate analysis using Cox-proportional hazards models, with withdrawal of azathioprine as time-dependent variable, was focused on differences between continuation of azathioprine, the period < 12 months after discontinuation of azathioprine- and the period > 12 months after discontinuation of azathioprine. Other co-variates in the multivariable model were age at presentation, sex, diagnosis (GPA versus MPA), route of cyclophosphamide administration (intravenous versus oral), duration of induction therapy, serum creatinine at presentation and BVAS at diagnosis. The proportional hazards assumptions were assessed using known predictors of relapse. For all comparisons, a two-sided p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS22 and GraphPad Prism version 5.01.

RESULTS

Patients

All main characteristics and outcomes of the original clinical studies are summarized in table 1. Of all 759 AAV patients, eventually 380 patients were included in the analysis (Fig 1). For this patients, baseline characteristics for each trial cohort are shown in table 2. Trial cohorts differed in age, gender distribution and disease severity, as reflected in the baseline criteria (Table 2).

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) mmol/l and initial median BVAS was 19 (13-25). Two hundred thirty-six (62%) patients had GPA, while 225 (59%) of patients were anti-PR3 positive.

The protocol-defined duration of azathioprine therapy varied from <12 months to 42 months and left to the discretion of the physicians thereafter with the exception of IMPROVE, where maintenance was withdrawn after 42 months (4,5,7,10,21,22).

Relapses

During follow up, 155 patients (40.8%) had a first relapse; 84 first relapses occurred during azathioprine-maintenance therapy (1 relapse per 117 patient months) and 71 after discontinuation of azathioprine. Of this 71 relapses, 49 occurred within 60 months after diagnosis (1 relapse/113 months) and 22 thereafter. During the first 12 months after stopping azathioprine, 20 relapses occurred (1 relapse/119 months). Twenty-nine relapses occurred between 12-60 months after discontinuation of azathioprine (1 relapse/186 months). Relapse free survival at 60 months after diagnosis was 65.3% for patients receiving azathioprine maintenance >18 months after diagnosis versus 55.0% for those who stopped maintenance ≤18 months (p 0.11) (Fig 3A). At all later time points of

Table 2 Baseline characteristics of all included patients in the individual studies.

	CYCA-CEREM	NORAM	MEPEX	CYCLOPS	WEGENT	IMPROVE
N	77	42	53	76	56	75
Sex: M/F	36/41	20/22	37/16	42/34	31/25	55/20
Age: *median (range)*	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/RL	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 (4-30)	20 (15-26)	20 (15-23)	24 (20-29)	19 (7-25)
seCreat: *median (range)*	146 (90-263)	84.5 (42-149)	724 (550-912)	162 (115-268)	105 (79-179)	177 (104-311)
Organ involvement: N (%)						
ENT	39 (51)*	42 (91)*	23 (53)	45 (59)	39 (70)	28 (37)
Pulm	44 (58)*	24 (51)*	18 (42)	45 (59)	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)

discontinuing azathioprine maintenance therapy, comparing duration > and ≤ 24 months, > and ≤ 36 months and > and ≤ 48 months, a numerically small and not statistical significant increase in relapses was found (Fig 3B-D). Relapse-free survival was lower in patients who were treated with intravenous cyclophosphamide compared to oral treatment (p 0.042) and lower in patients with PR3-ANCA compared to MPO-ANCA (p 0.011).

In a multivariate Cox-proportional hazard model, relapse risk was associated with successful discontinuation (without relapse) of azathioprine during a period of > 12 months (p 0.027). This means that when no relapse occurs ≤ 12 months after withdrawal of azathioprine, the relapse risk seems to be decreased during long term follow. Relapse risk was associated with the route of administration of cyclophosphamide, intravenous versus oral, HR 1.2 (95% CI 1.015-1.432, p 0.023). Also PR3 versus other ANCA status, HR 1.32 (95% CI 1.1-1.57) p 0.002 and creatinine at diagnosis HR 0.99 (95% CI 0.998-1.000) p 0.032 were significant covariates (Table 3).

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

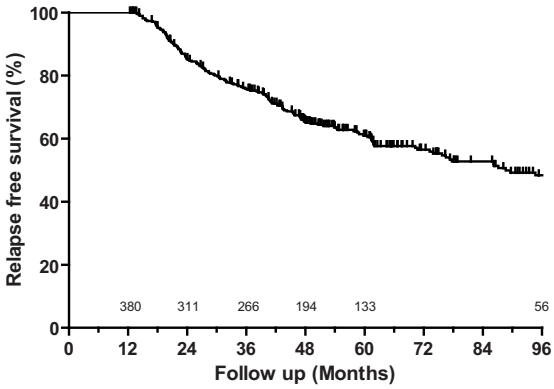

Figure 2A Relapse free survival during long term follow up, all patients.

Patients at risk (N=)

mths	12	24	36	48	60	96
N =	380	311	266	194	133	56

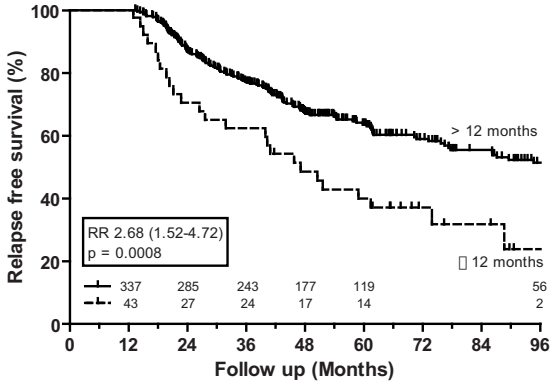

Figure 2B Relapse free survival during long term follow up,after withdrawal of azathioprine. P= 0.0008

Patients at risk (N=)

mths	12	24	36	48	60	96
> 12 mths	337	285	243	177	119	56
< 12 mths	43	27	24	17	14	2

Table 3 Multivariate Cox-proportional hazard analysis

	RR (95% CI)	p-value
Cyclophosphamide IV versus oral	1.206 (1.015-1.432)	0.023
PR3- versus other/none	1.316 (1.100-1.574)	0.002
Creatinine (diagnosis)	0.999 (0.998-1.000)	0.032
Azathioprine use (yes/no)	1.286 (0.870-1.901)	0.212
stopped < 12 months	1.183 (0.739-1.895)*	0.227
stopped > 12 months	0.570 (0.347-0.937)*	0.027

* as compared to current use

Table 4 Occurrence of at least one period of AE that can directly have been related to drug regimen

	NORAM > 6 mths	6-18 mths	19-24 mths	25-36 mths	37-48 mths	49-60 mths	P
Number of patients: n	44	46	78	58	74	81	
Infection: n (%)	2 (5)	20 (34)	19 (24)	19 (33)	27 (36)	19 (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
Trombotic events: n (%)	1 (2)	2 (4)	2 (3)	6 (10)	6 (8)	7 (9)	0.35

Secondary outcomes: mortality and ESRD.

Of the selected patients who survived the first year without experiencing any relapse, 94 patients (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 azathioprine duration, i.e. < 12 months, 12-18 months, 19-24 months, 25-36 months, 36-48 months and 49-60 months. Causes of death were mainly cardiovascular and infectious (Table 5).

Thirty-seven patients (10%) reached ESRD (for distribution, see also Fig 1A).

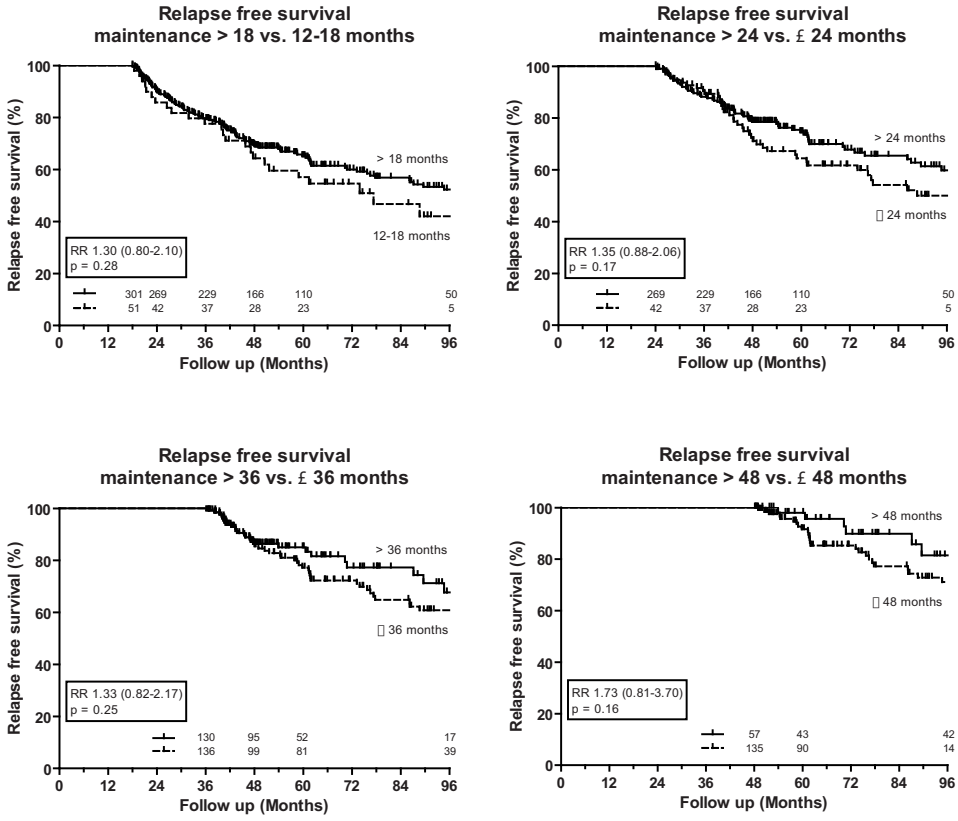

Figure 3 Relapse free survival curves for withdrawal after 18-48 months after diagnosis during longterm FU.

Adverse events

Serious adverse event that could have been related to immunosuppressive treatment were recorded during long term follow up. As depicted in Table 4, infection was the most documented adverse event but no difference in occurrence was found throughout the groups (p 0.07). Also, there was no difference for cardiovascular diseases (including cardiac events, stroke and revascularization-procedure, p 0.64), malignancy (p 0.24), diabetes mellitus (p 0.63), thrombotic events (p 0.35) and for bone disorders (p 0.73).

DISCUSSION

We have studied the relationship between duration of maintenance therapy and occurrence of relapses in an international cohort of 380 patients with AAV who were followed during and after termination of long term maintenance therapy. There was no significant difference in relapse-rate or relapse-free survival in patients who were treated beyond 12 months after diagnosis for different durations of treatment. Only patients in whom maintenance therapy was discontinued within 12 months after diagnosis were at higher risk of relapse. At all other analyzed time points from 18 months and beyond, a non-significant increase in relapse rate was observed in those patients who discontinued azathioprine maintenance therapy. Finally, in multivariate analysis, discontinuation of azathioprine maintenance therapy was associated with a slightly increased risk of relapses within 12 months. In addition intravenous administration of cyclophosphamide, anti-PR3 ANCA and higher serum creatinine at diagnosis were associated with relapse in multivariate analysis.
The concept of induction therapy at diagnosis followed by maintenance therapy to prevent relapse, described in 1983 by Fauci et al, has become the standard of care for AAV treatment (23). There is uncertainty as to the optimal duration of maintenance therapy after 18-24 months after diagnosis reported randomized trials has been relatively short (4,9).
After the findings of Slot et al, in which patients were followed 42 months, it seemed rational to treat patients at high risk for relapse- for instance those who remained ANCA-positive at time of remission- even longer than 18 months (18). However, concerns about maintenance and its duration do exist and controversy remains along with the proceeding of studies on maintenance agents and its duration. For instance, after rituximab-induction therapy, the occurrence of relapse at 18 months without any maintenance therapy was equal compared to cyclophosphamide induction followed by azathioprine maintenance therapy (20). 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 azathioprine 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 first hit' of induction treatment than due to maintenance therapy. The results of a multi-center remission of maintenance-study comparing short and long term courses of azathioprine maintenance therapy (REMAIN) may contribute to this debate.
In contrast to that, the IMPROVE-study showed that maintenance therapy for more than 20 months with mycofenolate mofetil was less effective in prevention of relapse compared to azathioprine (5). Outcome in relapse rate was adjusted for a diversity of pre-specified factors that could have influenced relapse-risk like diagnostic subtype, route of cyclophosphamide 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 finding suggests that maintenance therapy does have positive effects on relapse rate and that this effect may depend on the agent of choice (5). Comparing azathioprine to methotrexate as maintenance agent did not demonstrate differences in relapse-rate (21). Recently, rituximab maintenance therapy following cyclophosphamide induction therapy was superior in reducing relapse rate ($P < 0.0001$) compared to azathioprine in the MAINRITSAN-trial (24). Also, the RITAZEREM-trial, which is currently still recruiting patients, will test whether rituximab is superior to azathioprine in the prevention of exacerbations in AAV patients with relapsing disease (25).

The aforementioned inconsistent findings on different maintenance agents and its duration does lead to uncertainty about the optimal duration of maintenance. It also prompts questions whether maintenance therapy itself is related to outcome during long term follow up, or whether baseline characteristics of patient, disease or induction-agents perhaps are more important determinants in disease-course during long term follow up. This hypothesis fits the recently published data of the long term follow up of the CYCAZEREM, suggesting a trend to more relapses in the shorter cyclophosphamide exposure group (26). It also fits our present study, in which relapse rate was not different in any of the azathioprine-duration groups. Another important issue of debate is the role of long term use of low-dose steroids in the prevention of relapse, which until now is not evaluated extensively. 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 threatening physician; this situation makes it harder to make a statement on the other immunosuppressive agents. However, we also do know that there is considerable difference in belief as in the use of steroids between doctors, centers and between countries there is a 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. In our study, these adverse effects were equally divided and not statistically different between the groups on various duration 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 trails, mean baseline serum creatinine was unequally divided between these groups, so conclusions cannot be drawn from our findings on ESRD.
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 beyond the scope of the original studies. Data analysis was performed only a selection of 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 azathioprine duration. These follow up courses were not protocol determined and the reasons for continuing or changing management are not documented. Another major drawback is that we are not informed about steroids during follow up and this may be a confounder in our findings. Furthermore, data-collection may have not been optimal and for instance adverse events may have been underreported.
The comparison of heterogeneous trials which included different patient populations within the whole spectrum of AAV may lead to inconsistent findings. However, since this is also the population encountered in daily clinical practice, we think our findings can we applicable and are likely generalizable to patients with AAV in daily clinic.

In summary, we have found no evidence that extension of maintenance therapy with azathioprine maintenance therapy beyond 12-18 months after diagnosis is effective in relapse prevention. Intravenous administration of cyclophosphamide, 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 multi-center remission of maintenance-study comparing short and long term courses of azathioprine maintenance therapy are not yet published (REMAIN) but hopefully, the results or this large study will enable clinicians in daily practice to decide what maintenance agent to choose and for how long.

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