

ORIGINAL ARTICLE

A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies

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ABSTRACT

BACKGROUND

The primary systemic vasculitides usually associated with autoantibodies to neutrophil cytoplasmic antigens include Wegener's granulomatosis and microscopic polyangiitis. We investigated whether exposure to cyclophosphamide in patients with generalized vasculitis could be reduced by substitution of azathioprine at remission.

METHODS

We studied patients with a new diagnosis of generalized vasculitis and a serum creatinine concentration of 5.7 mg per deciliter (500 μ mol per liter) or less. All patients received at least three months of therapy with oral cyclophosphamide and prednisolone. After remission, patients were randomly assigned to continued cyclophosphamide therapy (1.5 mg per kilogram of body weight per day) or a substitute regimen of azathioprine (2 mg per kilogram per day). Both groups continued to receive prednisolone and were followed for 18 months from study entry. Relapse was the primary end point.

RESULTS

Of 155 patients studied, 144 (93 percent) entered remission and were randomly assigned to azathioprine (71 patients) or continued cyclophosphamide (73 patients). There were eight deaths (5 percent), seven of them during the first three months. Eleven relapses occurred in the azathioprine group (15.5 percent), and 10 occurred in the cyclophosphamide group (13.7 percent, $P=0.65$). Severe adverse events occurred in 15 patients during the induction phase (10 percent), in 8 patients in the azathioprine group during the remission phase (11 percent), and in 7 patients in the cyclophosphamide group during the remission phase (10 percent, $P=0.94$ for the comparison between groups during the remission phase). The relapse rate was lower among the patients with microscopic polyangiitis than among those with Wegener's granulomatosis ($P=0.03$).

CONCLUSIONS

In patients with generalized vasculitis, the withdrawal of cyclophosphamide and the substitution of azathioprine after remission did not increase the rate of relapse. Thus, the duration of exposure to cyclophosphamide may be safely reduced.

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N Engl J Med 2003;349:36-44.

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THE MOST COMMON PRIMARY SYSTEMIC vasculitis syndromes — Wegener's granulomatosis, microscopic polyangiitis, and vasculitis limited to the kidneys — are associated with circulating autoantibodies to neutrophil cytoplasmic antigens (ANCA).¹⁻³ It has been suggested that they be grouped together as ANCA-associated vasculitis because of their histologic similarities, the absence of immune deposits in all of them, the potential contribution of ANCA to their pathogenesis, and their similar responses to immunosuppressive therapy.^{2,4-12} Renal involvement is common and is typically manifested as rapidly progressive glomerulonephritis; it results in either death or end-stage renal failure within two years in more than 40 percent of patients.^{4,6,13,14}

We have previously subclassified ANCA-associated vasculitis according to the severity and extent of disease at presentation and have defined generalized vasculitis as vasculitis that threatens vital-organ function.² The standard therapy for generalized ANCA-associated vasculitis has comprised at least one year of corticosteroid and oral cyclophosphamide therapy.^{2,15-19} The resultant exposure to cyclophosphamide causes hemorrhagic cystitis and increases the risk of bladder cancer and lymphoproliferative disease, myelodysplasia, and infertility. The vasculitis returns in 50 percent of patients, often after the reduction or discontinuation of therapy.^{14,17-19} Azathioprine is less toxic than cyclophosphamide and has been used as an alternative immunosuppressive agent for the maintenance of remission in patients with vasculitis.^{14,20,21} We undertook a study to evaluate whether exposure to cyclophosphamide could be reduced in patients with generalized ANCA-associated vasculitis by the early substitution of azathioprine at the time of remission. Relapse was the primary outcome measure.^{2,5}

METHODS

STUDY PATIENTS

Patients were recruited from 39 hospitals in 11 European countries. The study was approved by the local ethics committees, and all patients gave written informed consent.

STUDY DESIGN

All patients received the same remission-induction therapy, consisting of cyclophosphamide and prednisolone. Those patients in whom remission had been achieved by three months, or between three

and six months, were randomly assigned to treatment with azathioprine as a substitute for cyclophosphamide (azathioprine group) or to continued cyclophosphamide therapy (cyclophosphamide group). Twelve months after study entry, the patients in the cyclophosphamide group were switched to the same azathioprine regimen as the azathioprine group was receiving and continued to receive this regimen until the end of the study, 18 months after entry.²

ELIGIBILITY CRITERIA

Criteria for inclusion in the study included a diagnosis of Wegener's granulomatosis, microscopic polyangiitis, or renal-limited vasculitis; renal involvement, other threatened loss of function of a vital organ (lung, brain, eye, motor nerve, or gut), or both; and ANCA positivity. ANCA-negative patients were eligible for enrollment in the study if there was histologic confirmation of vasculitis.^{1,5,22,23} Criteria for exclusion were the use of a cytotoxic drug within the previous year; the coexistence of another multisystem autoimmune disease; hepatitis B e antigenemia, hepatitis C, or human immunodeficiency virus infection; a serum creatinine concentration of more than 5.7 mg per deciliter (500 μ mol per liter); cancer; pregnancy; and an age of less than 18 years or more than 75 years.

DRUG REGIMENS

Both groups received oral cyclophosphamide (2 mg per kilogram of body weight per day) and prednisolone (initially 1 mg per kilogram per day, with the dose tapered to 0.25 mg per kilogram per day by 12 weeks).² The dose of cyclophosphamide was reduced by 25 mg for patients older than 60 years of age, and cyclophosphamide therapy was discontinued if the patient had a white-cell count of less than 4000 per cubic millimeter. After randomization, patients received either continued cyclophosphamide therapy (1.5 mg per kilogram per day) or azathioprine (2 mg per kilogram per day), with the same dose of prednisolone (10 mg per day). Beginning at 12 months, both groups received azathioprine (1.5 mg per kilogram per day) and prednisolone (7.5 mg per day). Prophylaxis against corticosteroid-induced gastritis, fungal infection, and *Pneumocystis carinii* pneumonia was recommended but not mandatory.

EVALUATIONS

Study assessments were performed after 0, 1.5, 3, 6, 9, 12, 15, and 18 months and at the time of relapse, if it occurred. The assessments included a complete

blood count and measurement of the erythrocyte sedimentation rate, C-reactive protein, alanine aminotransferase, serum creatinine, and glucose. The glomerular filtration rate was measured at entry, at

the time of remission, and at the end of the study. Disease activity was measured in terms of the Birmingham Vasculitis Activity Score and the Disease Extension Index.²⁴⁻²⁶ The Birmingham Vasculitis Activity Score includes values for 64 predefined items derived from clinical or radiologic evaluation in 10 organ systems.^{24,25} Each item carries a weight (ranging from 1 to 9), and an item is scored if the investigator believes it to be present and caused by active vasculitis. Positive scores are subclassified as scores for new or worse disease since the previous examination (range of scores, 0 to 63, with higher scores indicating more active disease) or as scores for persistent disease (range of scores, 0 to 36). Cumulative damage from any cause since the onset of disease was scored on the Vasculitis Damage Index at 0, 6, 12, and 18 months.²⁷ The range of scores on this index is 0 to 63, with higher scores indicating greater damage. The Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) was administered at each assessment.^{28,29} Adverse events were graded according to predefined criteria as mild, moderate, severe, or life-threatening.

DISEASE DEFINITIONS

Diagnostic definitions were adapted from the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis⁴ and a previous European Union study.⁵ Remission was defined as a Birmingham Vasculitis Activity Score that indicated the absence of signs of new or worse disease activity, with persistent disease activity for no more than one item. Major relapse was defined by the recurrence or first appearance of at least 1 of the 24 items on the Birmingham Vasculitis Activity Score that are indicative of threatened function of a vital organ (the kidney, lung, brain, eye, motor nerve, or gut) attributable to active vasculitis. Minor relapse was defined by the recurrence or first appearance of at least three other items in the Birmingham Vasculitis Activity Score. Determinations of remission and relapse were made by the investigator and validated retrospectively by an independent observer.

STATISTICAL ANALYSIS

Randomization was performed centrally with the use of permuted blocks of four within each country, with stratification according to diagnosis. Primary data were collected in record books and submitted for centralized computer entry. The data were validated against the record books before analysis (with the use of SPSS statistical software, ver-

Table 1. Characteristics of the Patients at Randomization.*

Characteristic	Azathioprine Group (N=76)	Cyclophosphamide Group (N=79)	All Patients (N=155)
Age — yr			
Mean	57	59	58
Range	20–76	20–77	20–77
Female sex — no. (%)	36 (47)	46 (58)	82 (53)
Diagnosis — no. (%)			
Wegener's granulomatosis	46 (61)	49 (62)	95 (61)
Microscopic polyangiitis	30 (39)	30 (38)	60 (39)
PR3-ANCA-positive — no. (%)	41 (54)	47 (59)	88 (57)
MPO-ANCA-positive — no. (%)	30 (39)	27 (34)	57 (37)
No. of systems involved			
Mean	4	4	4
Range	1–9	1–8	1–9
Renal involvement — no. (%)	71 (93)	75 (95)	146 (94)
Ear, nose, and throat involvement — no. (%)	39 (51)	38 (48)	77 (50)
Lung involvement — no. (%)	44 (58)	41 (52)	85 (55)
Birmingham Vasculitis Activity Score for new or worse disease			
Mean score	18.0	19.9	18.9
95% CI	16.0–20.0	17.7–22.2	17.5–20.4
Disease Extension Index			
Mean score	6.1	5.9	6.1
95% CI	5.4–6.9	5.1–6.8	5.5–6.6
Glomerular filtration rate — ml/min			
Mean	53.4	45.1	49.2
95% CI	45.4–61.5	37.6–52.6	43.7–54.6
C-reactive protein level — mg/liter			
Mean	64.2	70.1	67.3
95% CI	47.6–80.8	50.2–90.0	54.4–80.1
Erythrocyte sedimentation rate — mm/hr			
Mean	74.6	77.9	76.3
95% CI	64.5–84.7	69.6–86.3	69.9–82.7
Remission — no. (%)			
By 3 mo	58 (76)	61 (77)	119 (77)
By 6 mo	71 (93)	73 (92)	144 (93)

* Birmingham Vasculitis Activity Scores for new or worse disease range from 0 to 63, with higher scores indicating more active disease. Scores on the Disease Extension Index range from 0 to 21, with higher scores indicating more extensive disease. PR3-ANCA denotes anti-proteinase 3 antibodies, MPO-ANCA antimyeloperoxidase antibodies, and CI confidence interval.

sion 9) by two data managers who had sole access to the data.³⁰

The primary end point was relapse, either major or minor. The predicted relapse rate for the cyclophosphamide group was 25 percent.^{14,19,20} The study was designed to detect an increase in the relapse rate in the azathioprine group of more than 20 percentage points — that is, from 25 percent to at least 45 percent. A total of 146 patients were required in order to achieve a significance level of 0.05 and a power of 0.8. The effect of treatment on time to relapse was examined by Kaplan–Meier analysis with the use of the log-rank test. The demographic characteristics of the two groups were compared; categorical variables were analyzed by Fisher’s exact test, and their effects on relapse were assessed as covariants in the Kaplan–Meier test.

The two groups were compared in terms of the secondary end points reached between the time of remission and the end of the study. The rates of adverse events were compared with the use of two-by-two tables and Fisher’s exact test. Changes in the glomerular filtration rate were assessed by analysis of covariance within groups, and linear-regression analysis was used to measure the correlations and the differences between groups. The areas under the curve for the Birmingham Vasculitis Activity Score were compared with the use of Student’s t-test after logarithmic transformation. The values on the Vasculitis Damage Index were compared with the use of the Mann–Whitney U test. The mean scores on the SF-36 were calculated for each of the eight dimensions according to the Likert method of summated ratings, and the groups were compared in terms of the changes in the scores over time with the use of repeated-measures analysis. C-reactive protein levels and erythrocyte sedimentation rates were compared with the use of Student’s t-test. All tests of significance were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. No interim analyses were performed.

RESULTS

PATIENTS

A total of 158 patients were registered, 3 declined further participation, and 155 entered the trial. There were no significant differences between the two groups in demographic, clinical, or laboratory features at the time of randomization (Table 1). Histologic confirmation of the diagnosis was available for 132 patients and was subjected to central re-

view.³¹ Clinical remission was achieved in 144 of the patients (93 percent) — by three months in 119 patients (77 percent) and between three and six months in 25 patients (16 percent). These patients were randomly assigned to cyclophosphamide (73 patients) or azathioprine (71 patients).

DEATHS AND WITHDRAWALS

Seven patients died during the remission-induction phase (two from pneumonia, three from pulmonary vasculitis and infection, and two from stroke), and one patient died (from stroke) during the remission-maintenance phase. One patient was withdrawn from the study during the remission-induction phase, and five patients were withdrawn during the remission-maintenance phase — two in the cyclophosphamide group (one at 6 months and one at 13 months) and three in the azathioprine group (one at 7 months, one at 12 months, and one at 13 months). Three of these patients were lost to follow-up, and the other three were withdrawn from the study by their physicians.

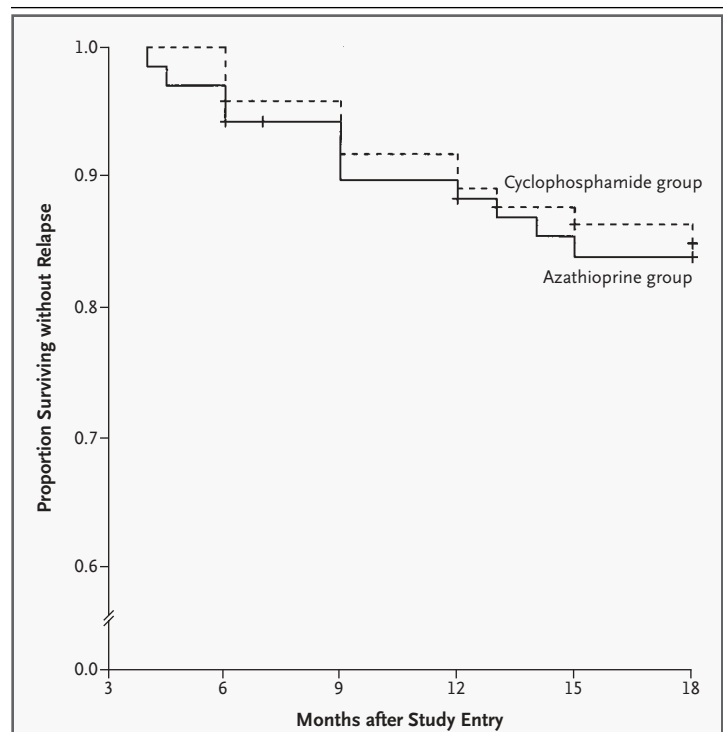


Figure 1. Kaplan–Meier Analysis of the Time to First Relapse in the Azathioprine and Cyclophosphamide Groups.

Plus signs represent withdrawals or deaths.

RELAPSE

Eleven patients in the azathioprine group had relapses (15.5 percent [95 percent confidence interval, 6.9 to 24.0]), as did 10 patients in the cyclophosphamide group (13.7 percent [95 percent confidence interval, 5.6 to 21.7]; $P=0.65$; difference, 1.8 percentage points [95 percent confidence interval, -9.9 to 13.0]) (Fig. 1). Five patients in each group had a major relapse. The mean C-reactive protein level at relapse was 26.1 mg per liter (95 percent confidence interval, 0 to 55), and the mean erythrocyte sedimentation rate at relapse was 49 mm per hour (95 percent confidence interval, 23 to 75). Relapse was less common among patients with microscopic polyangiitis (4 of 52 patients [8 percent]) than among those with Wegener's granulomatosis (17 of 92 patients [18 percent], $P=0.03$). No other variables at entry influenced the rate of relapse.

ADVERSE EVENTS

A total of 218 adverse events were reported in 84 patients (Table 2). Fifty-five percent of patients (85

of 155) had at least one episode of neutropenia. Severe or life-threatening events occurred in 15 patients (10 percent) during the remission-induction phase, in 8 patients in the azathioprine group during the remission-maintenance phase (11 percent), and in 7 patients in the cyclophosphamide group during the remission-maintenance phase (10 percent; $P=0.94$). Of 33 infections, 17 (52 percent) were associated with concurrent neutropenia. Allergy to azathioprine, manifested by fevers, chills, and a rash, resulted in its discontinuation in five patients (7 percent).

RENAL FUNCTION

There were similar increases in the glomerular filtration rate from study entry to 18 months in the two groups: an increase of 17.5 ml per minute (95 percent confidence interval, 11.9 to 23.1) in the azathioprine group ($r^2=0.57$) and an increase of 23.5 ml per minute (95 percent confidence interval, 18.2 to 29.0) in the cyclophosphamide group ($r^2=0.56$) (Fig. 2). End-stage renal failure developed in two patients in each group.

Table 2. Adverse Events.

Variable	Induction Phase (0–3 Mo)		Remission Phase (4–18 Mo), Azathioprine Group (N=71)		Remission Phase (4–18 Mo), Cyclophosphamide Group (N=73)		Entire Study Period
	Mild or Moderate	Severe or Life- Threatening	Mild or Moderate	Severe or Life- Threatening	Mild or Moderate	Severe or Life- Threatening	
	<i>number of events (percent)</i>						
Leukopenia	30	7	21	1	32	3	94
Anemia	0	0	2	0	1	0	3
Diabetes	3	2	2	1	2	0	10
Infection	3	4	9	4	10	3	33
Bone fracture	0	0	0	2	0	2	4
Gastrointestinal event	3	0	3	0	2	3	11
Cardiovascular event	0	4	1	2	1	2	10
Cystitis	0	0	1	0	3	0	4
Allergy	3	0	4	1	2	0	10
Amenorrhea	0	0	0	1	0	2	3
Alopecia	3	0	0	0	2	0	5
Psychiatric event	3	0	0	0	0	0	3
Other adverse event	7	1	6	0	14	0	28
Any adverse event	55	18	49	12	69	15	218
≥1 Event	52 (34)	15 (10)	29 (41)	8 (11)	32 (44)	7 (10)	84 (54)

BIRMINGHAM VASCULITIS ACTIVITY SCORES

The mean scores for new or worse disease decreased promptly with the initiation of remission-induction therapy (Fig. 3A). The mean scores for persistent disease decreased more slowly and remained low during the trial, without significant differences between the groups (Fig. 3B).

VASCULITIS DAMAGE INDEX

At entry into the trial, most patients already had damage as a result of the disease; the mean score on the Vasculitis Damage Index was 1.3 (95 percent confidence interval, 1.0 to 1.6), reflecting at least one item indicating damage per patient. There was a significant increase in damage over the course of the trial (mean score at 18 months, 2.5 [95 percent confidence interval, 2.1 to 3.0]; $P=0.003$). There was no difference between the two groups in the increase in damage score during the trial.

SF-36

At entry, the mean values for measures of physical and mental health on the SF-36 were all more than 30 percent lower than the norm for the United Kingdom population, with the values for the perceived limitation on role-related activities due to physical problems more than 70 percent lower than the norm. Values for physical health measures remained substantially below the norm during the remission phase. Values for mental health measures improved and were an average of 14 percent lower than the norm at remission. The averages for the whole cohort increased significantly with time throughout the trial ($P<0.001$). No significant differences between groups were observed in the SF-36 score.

INFLAMMATORY MARKERS

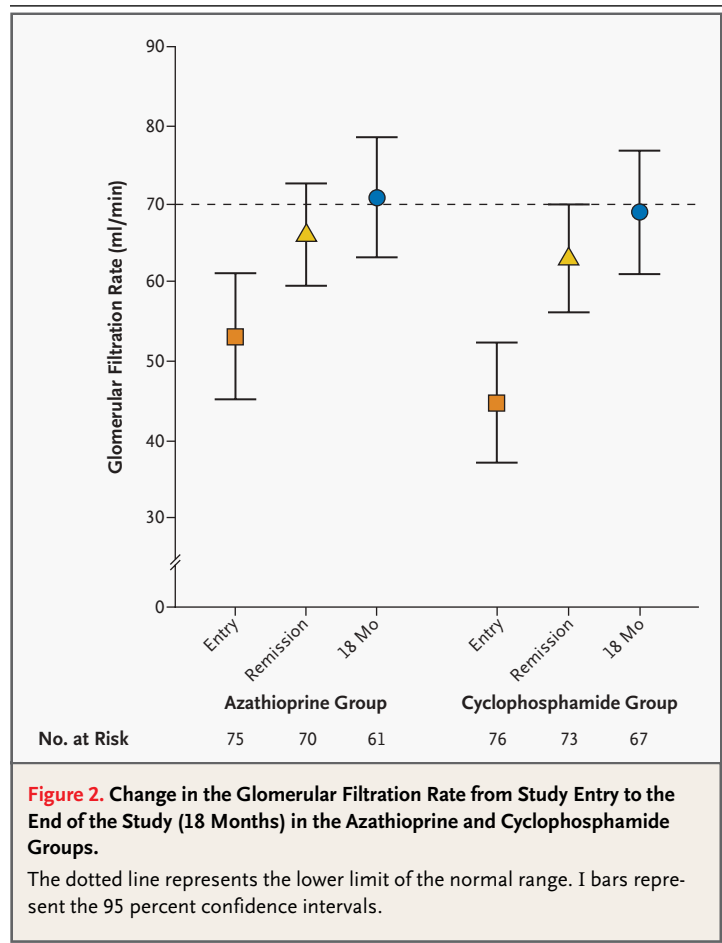
No significant differences between groups were observed in the C-reactive protein levels or the erythrocyte sedimentation rate.

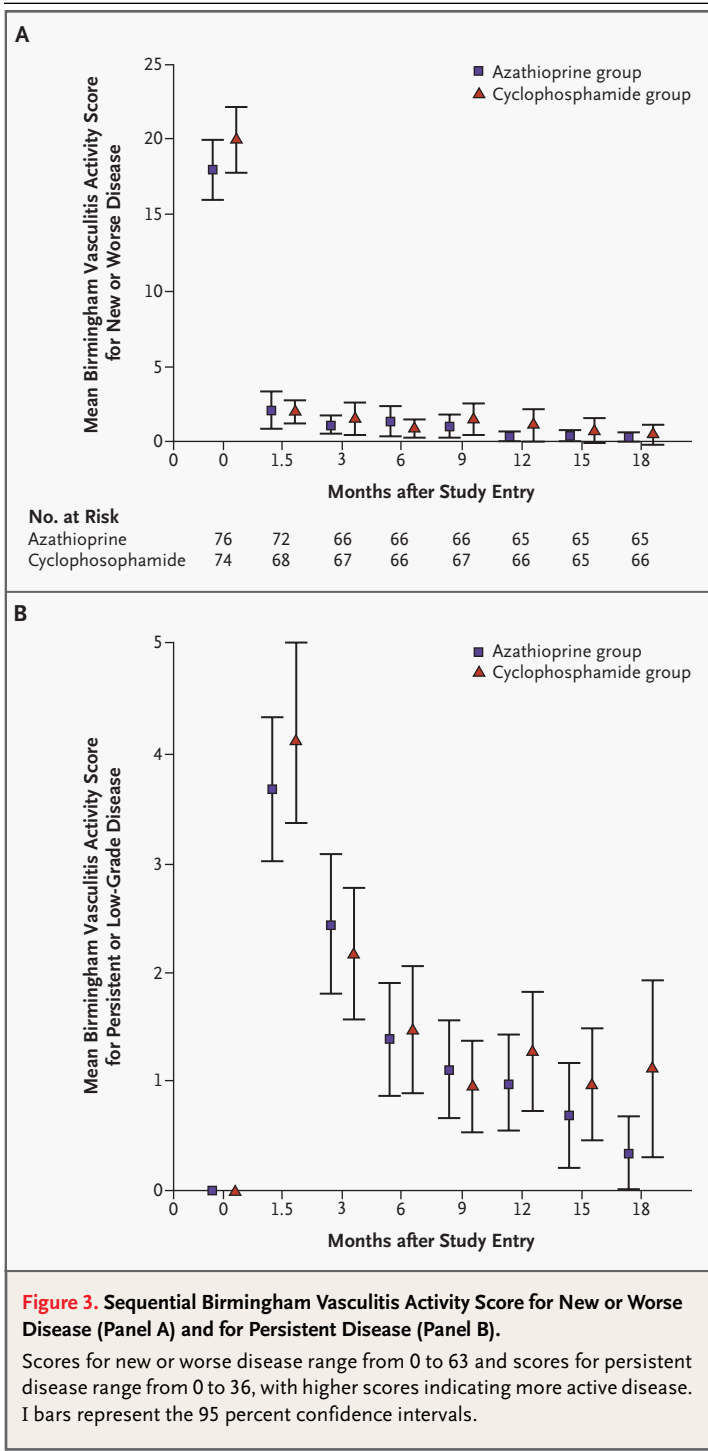
DISCUSSION

We investigated the optimal initial duration of cyclophosphamide therapy for ANCA-associated systemic vasculitis. The early substitution of azathioprine for cyclophosphamide during remission — usually at three months — resulted in a rate of relapse that was similar to that in the group receiving the control regimen of 12 months of cyclophosphamide therapy. Thus, the initial duration of exposure to cyclophosphamide and the risks of such treatment in

terms of cancer and infertility can be safely reduced in patients with generalized vasculitis. The results support the concept of aggressive treatment for active disease and lower-intensity therapy for the maintenance of remission. The possible need for further cyclophosphamide treatment for late relapse adds to the importance of minimizing the initial level of exposure.

In our unblinded trial, the determination of remission and relapse by the investigator was a potential source of bias. However, the semi-objective scores for vasculitis activity and laboratory measurements of disease activity were similar in both groups at the start of the remission phase of the trial, and increases in these values at the time of relapse were also similar in both groups. The observed difference in the relapse rate was small — 1.8 percentage points — and the 95 percent confidence interval for this difference (−9.9 to 13.0 percentage points) indicates that although the real difference could be





larger, it would still be less than the 20 percentage points that the study was powered to detect.

An increase in the relapse rate in the azathioprine group after 18 months cannot be ruled out, but previous longer-term experience with azathio-

prine suggests that any increase is unlikely to be large.²¹ Relapse of disease has been common after the discontinuation of therapy in patients with Wegener's granulomatosis; we are currently assessing the optimal duration of remission-maintenance therapy.^{18,32} The relapse rate of 15 percent was lower than that predicted on the basis of previous trials and suggests that the subgroup we studied had a lower relapse rate than other subgroups of patients with vasculitis. Similarly low rates have been reported among patients with renal vasculitis.³³ The higher relapse rate among patients with Wegener's granulomatosis may reflect the additional presence of granulomatous disease and the colonization of diseased respiratory mucosa with respiratory pathogens, such as *Staphylococcus aureus*.^{32,34}

We excluded patients with advanced renal failure and those whose vital-organ function was not threatened. Renal vasculitis was the most common form of organ involvement, occurring in 94 percent of the patients in our study. Induction therapy with daily oral cyclophosphamide and oral prednisolone was effective: remission was achieved in 77 percent of patients by three months and in 93 percent by six months. Patients in whom remission was not achieved had either died or been lost to follow-up, and no patient had primary treatment failure. The rate and speed of remission were greater than those reported in previous studies and may have been influenced by the exclusion of patients with severe disease and the inclusion of patients with a new diagnosis and primarily renal involvement.^{17,35} The good results should be balanced against the toxicity of this regimen: five of the seven deaths that occurred during the induction phase were related to treatment. Daily oral cyclophosphamide was the preferred induction therapy for this group of patients at the time the trial was designed; subsequent reports have indicated that regimens involving the intermittent, pulsed administration of cyclophosphamide are safer but are associated with a higher rate of relapse.³⁵⁻³⁸

Adverse events were frequent, and neutropenia caused by cyclophosphamide or azathioprine treatment occurred in 55 percent of the patients, despite the inclusion in the protocol of advice designed to reduce the risk of neutropenia. Because older age and renal failure predispose patients to myelosuppression, this complication is common in patients with vasculitis: the mean age of our patients was 58 years, and the mean glomerular filtration rate at entry was 49.2 ml per minute. Other cyclophosphamide-related complications, including hemorrhag-

ic cystitis, alopecia, and amenorrhea, were rare. Hypersensitivity reactions to azathioprine led to its discontinuation in five patients, and the reactions were initially difficult to differentiate from a relapse of vasculitis. The study was not designed to detect a difference between groups in the rate of adverse events, and a reduction in the rate of late toxic effects of cyclophosphamide could not have been revealed because of the relatively short duration of the trial.

Renal outcomes were generally good, with renal failure occurring in only four patients (3 percent). There were large increases in the glomerular filtration rate, most of which occurred during the first three months. These outcomes suggest a new standard of care and highlight the importance of referral before renal failure develops, since after renal failure has occurred, outcomes are much poorer.³⁹ Longer follow-up is required in order to determine the stability of renal recovery, particularly in patients whose renal function remains impaired.

The Birmingham Vasculitis Activity Score demonstrated sensitivity to change in parallel with laboratory measures of disease activity. The persistence of disease after induction therapy highlights a suboptimal response to treatment in a minority of patients.⁴⁰ The scores on the Vasculitis Damage Index demonstrated the frequent presence of damage at presentation; such damage indicates that there is a delay between the development of symptoms and diagnosis in patients with vasculitis. The score on this index increased during the trial despite the fact that disease activity was controlled, reflecting the consequences of vasculitic inflammation and of ad-

verse events. Further research is required to clarify the mechanisms of progressive damage, which are potential new targets of therapy. The SF-36 scores for perceived illness were extremely low at presentation, and these scores remained below normal levels at the end of the study. It is unclear whether this finding reflects a slow healing process, poor rehabilitation, vasculitic damage, subclinical disease activity, or ongoing toxic effects of the drugs.

Azathioprine was selected for use in this study because it was already widely used for the maintenance of remission in patients with renal vasculitis. Alternative therapies that merit further consideration include methotrexate, mycophenolate mofetil, leflunomide, cyclosporine, and blockade of tumor necrosis factor α .⁴¹⁻⁴⁵ The grouping of ANCA-associated vasculitides will simplify and expedite diagnosis and the initiation of remission-induction treatment in patients with rapidly evolving vital-organ disease, although improved treatments will be required to prevent relapse. Our findings indicate that it is possible to reduce patients' exposure to cyclophosphamide and its toxic effects without increasing the rate of relapse. These findings have immediate relevance for the daily management of vasculitis.

Supported by contracts (BMH1-CT93-1078, CIPD-CT94-0307, BMH4-CT97-2328, and IC20-CT97-0019) with the European Union. Dr. Tesar reports having received consulting or lecture fees from GlaxoSmithKline and AstraZeneca.

We are indebted to Jo Hermans and J.C. van Houwelingen (Leiden, the Netherlands) and Paul Landais (Paris) for advice on statistical analysis; to Jane Thorogood (London), the biostatistician for the trial; to Helen Talbot (Edinburgh, United Kingdom) for software design; to Fred Compton (London) for data management; and to Lucy Jayne (London), the trial administrator.

APPENDIX

In addition to the authors, the following investigators participated in the Cyclophosphamide versus Azathioprine as Remission Maintenance Therapy for ANCA-Associated Vasculitis Study. **Belgium:** Erasmus Hospital, Brussels — D. Abramowicz, M. Wissing; Universitaire Ziekenhuis, Leuven — D. Blockmans; Edith Cavell Medical Institute, Brussels — P. Madhoun; AZ VUB, Brussels — J. Sennesael; IMC de Tournai, Tournai — J. Stolar. **Czech Republic:** Charles University Hospital, Prague — V. Chabova, I. Rychlik. **Finland:** University of Helsinki, Helsinki — C. Grönhagen-Riska. **France:** Hôpital Necker, Paris — P. Lesavre; Centre Hospitalier, Valenciennes — P. Vanhille. **Ireland:** St. James Hospital, Dublin — C. Feighery. **Germany:** Heidelberg University Hospital, Heidelberg — O. Hergesell; Klinikum Mannheim, Mannheim — F. van der Woude, R. Nowack; Rheumaklinik, Bad Bramstedt — W. Schmitt; Heinrich Heine Universität, Düsseldorf — M. Schneider, C. Specker; Klinikum Nürnberg, Nürnberg — H. Rupperecht, P. Weber, S. Weidner. **The Netherlands:** University Hospital, Groningen — C. Kallenberg, C. Stegeman; Eemland Hospital, Amersfoort — E. van Gorp; Leiden University Medical Center, Leiden — C. Siegert, C. Verburgh. **Spain:** Hospital Germans Trias i Pujol, Badalona — A. Serra; Hospital Doctor Josep Trueta, Girona — M. Valles; Hospital Princes d'Espanya, Llobregat — R. Poveda; Fundació Puigvert, Barcelona — J. Ballarin. **Sweden:** Huddinge University Hospital, Huddinge — A. Bruchfeld; Danderyds Sjukhus, Danderyds — G. Germanis; University Hospital of Lund, Lund — D. Selga; Karolinska Sjukhuset, Stockholm — Z. Heigl, I. Lundberg, E. Svenungsson. **United Kingdom:** Southmead Hospital, Bristol — P. Mathieson; Ipswich Hospital, Ipswich — R. Watts; Leicester General Hospital, Leicester — J. Feehally; Royal Free Hospital, London — A. Burns; Western General Hospital, Edinburgh — R. Luqmani; Queen Elizabeth II Hospital, Birmingham — D. Adu, C. Savage.

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