

ORIGINAL ARTICLE

Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis

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ABSTRACT

BACKGROUND

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N Engl J Med 2008;359:2790-803.
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Current standard therapy for Wegener's granulomatosis and microscopic polyangiitis combines corticosteroids and cyclophosphamide to induce remission, followed by a less toxic immunosuppressant such as azathioprine or methotrexate for maintenance therapy. However, azathioprine and methotrexate have not been compared with regard to safety and efficacy.

METHODS

In this prospective, open-label, multicenter trial, we randomly assigned patients with Wegener's granulomatosis or microscopic polyangiitis who entered remission with intravenous cyclophosphamide and corticosteroids to receive oral azathioprine (at a dose of 2.0 mg per kilogram of body weight per day) or methotrexate (at a dose of 0.3 mg per kilogram per week, progressively increased to 25 mg per week) for 12 months. The primary end point was an adverse event requiring discontinuation of the study drug or causing death; the sample size was calculated on the basis of the primary hypothesis that methotrexate would be less toxic than azathioprine. The secondary end points were severe adverse events and relapse.

RESULTS

Among 159 eligible patients, 126 (79%) had a remission, were randomly assigned to receive a study drug in two groups of 63 patients each, and were followed for a mean (\pm SD) period of 29 ± 13 months. Adverse events occurred in 29 azathioprine recipients and 35 methotrexate recipients ($P=0.29$); grade 3 or 4 events occurred in 5 patients in the azathioprine group and 11 patients in the methotrexate group ($P=0.11$). The primary end point was reached in 7 patients who received azathioprine as compared with 12 patients who received methotrexate ($P=0.21$), with a corresponding hazard ratio for methotrexate of 1.65 (95% confidence interval, 0.65 to 4.18; $P=0.29$). There was one death in the methotrexate group. Twenty-three patients who received azathioprine and 21 patients who received methotrexate had a relapse ($P=0.71$); 73% of these patients had a relapse after discontinuation of the study drug.

CONCLUSIONS

These results do not support the primary hypothesis that methotrexate is safer than azathioprine. The two agents appear to be similar alternatives for maintenance therapy in patients with Wegener's granulomatosis and microscopic polyangiitis after initial remission. (ClinicalTrials.gov number, NCT00349674.)

COMBINED CORTICOSTEROID AND CYCLOPHOSPHAMIDE therapy remains the standard care for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, despite the potential risk of adverse events, particularly with the long-term use of cyclophosphamide.^{1,2} Moreover, even after induction with daily oral or pulse intravenous cyclophosphamide therapy, relapse rates remain as high as 15% at 12 months³ and reach 38% at 30 months.⁴

A decisive step in the approach to the treatment of Wegener's granulomatosis and microscopic polyangiitis was the development of a staged induction-maintenance strategy to reduce cumulative exposure to cyclophosphamide. This strategy uses cyclophosphamide to induce remission, followed by a less toxic immunosuppressant. A randomized trial in which 30 patients with various systemic vasculitides were assigned to receive remission maintenance therapy with azathioprine or oral cyclophosphamide showed similar relapse rates with the two agents and a nonsignificant reduction in rates of adverse events with oral cyclophosphamide.⁵ The similar safety and efficacy of azathioprine and continued cyclophosphamide maintenance therapy for up to 18 months in non-life-threatening Wegener's granulomatosis and microscopic polyangiitis were demonstrated in a large, randomized, multicenter trial.⁶ Although the results of uncontrolled studies suggested that methotrexate might provide effective maintenance therapy for patients with Wegener's granulomatosis, with a toxicity profile that may be as good as or even better than that of azathioprine,⁷⁻⁹ it remains unclear whether one of these two agents might be safer or more effective than the other.

We report the results of a prospective, multicenter, randomized, open-label clinical trial (the Wegener's Granulomatosis-Entretien [WEGENT] trial) designed to evaluate the safety and efficacy of azathioprine as compared with methotrexate, combined with prednisone, as maintenance treatment for patients who had a complete remission of Wegener's granulomatosis or microscopic polyangiitis with pulse intravenous cyclophosphamide and corticosteroids.

METHODS

STUDY DESIGN

The trial was conducted from November 1998 through February 2005 in university and general

hospitals in France and Belgium. The study protocol was developed by the investigator advisory committee of the French Vasculitis Study Group and was approved by the study group's ethics committee and review board. Study drugs were purchased by the patients from local pharmacies, and the cost of these drugs was reimbursed by the French National Health System. All patients provided written informed consent. Study data were collected, entered into a central database, and analyzed by the investigators.

Patients older than 18 years of age who had newly diagnosed Wegener's granulomatosis or microscopic polyangiitis were screened for eligibility. Patients with Wegener's granulomatosis had to meet the classification criteria of the American College of Rheumatology¹⁰ or those of the Chapel Hill nomenclature,¹¹ which includes "granulomatous inflammation of the respiratory tract"; the latter criterion was considered to be met when crusting rhinitis, destructive sinonasal disease, subglottic stenosis, lung nodules, or a combination of these conditions were present. In addition, patients with Wegener's granulomatosis had to have renal disease, involvement of at least two organs or systems, or involvement of one organ or system and constitutional symptoms (i.e., temperature above 38°C, weight loss exceeding 3 kg within the previous month, and diffuse arthralgias or myalgias). Patients with microscopic polyangiitis, defined according to the Chapel Hill criteria,¹¹ and at least one item on the five-factor score indicating a poor-prognosis^{12,13} were also eligible. Also required for eligibility was histologic confirmation of the diagnosis or positive results of serologic testing for ANCA. ANCA was tested by means of indirect immunofluorescence, enzyme-linked immunosorbent assay (ELISA) for myeloperoxidase and proteinase-3 specificity, or both.

Exclusion criteria were the use of corticosteroids for more than 1 month before the initiation of cyclophosphamide therapy, the coexistence of another systemic disease, cancer (unless it had been in complete remission for more than 3 years), human immunodeficiency virus or hepatitis B or C virus infection, a contraindication for taking the study medications, pregnancy or the absence of contraception in premenopausal women, and mental or physical disabilities abrogating the patient's ability to provide written informed consent.

TREATMENT PROTOCOL

All patients received identical therapy for the induction of remission. The corticosteroid regimen comprised a daily intravenous pulse of methylprednisolone (15 mg per kilogram of body weight) for 3 days, followed by oral prednisone (1 mg per kilogram per day) for 3 weeks, which was then progressively tapered according to a predefined schedule to obtain an average daily dose of 12.5 mg at 6 months and 5 mg per day at 18 months, with complete discontinuation of treatment after the 24th month. The first three pulses of cyclophosphamide (at a dose of 0.6 g per square meter of body-surface area) were administered every 2 weeks, then every 3 weeks (at a dose of 0.7 g per square meter) until remission, followed by three additional consolidation pulses (at a dose of 0.7 g per square meter) at the same 3-week interval. The cyclophosphamide dose was reduced to 0.5 g per square meter in patients older than 65 years of age, patients with an estimated creatinine clearance of less than 30 ml per minute, or both. All patients received mesna with each pulse for protection against hemorrhagic cystitis; trimethoprim-sulfamethoxazole (80 mg of trimethoprim plus 400 mg of sulfamethoxazole per day or 160 mg of trimethoprim plus 800 mg of sulfamethoxazole every other day) or, in patients with intolerance to trimethoprim-sulfamethoxazole, aerosolized pentamidine (300 mg every 3 to 4 weeks) to prevent *Pneumocystis jirovecii* pneumonia; potassium supplementation; and calcium, vitamin D₃, and oral bisphosphonates, when indicated. Patients who did not enter remission within the first 6 months or who had a relapse during the pulse-cyclophosphamide consolidation period were not randomly assigned to a treatment group and were treated according to best medical judgment.

Patients who had a remission were randomly assigned after the third consolidation pulse of cyclophosphamide to receive oral maintenance therapy with azathioprine (2.0 mg per kilogram per day) or methotrexate (0.3 mg per kilogram per week initially and progressively increased every week by 2.5 mg, to 25 mg per week), starting 2 to 3 weeks after the last pulse. Randomization was performed at a central site according to permuted blocks of six. At the end of the scheduled 12-month period of maintenance therapy, azathioprine or methotrexate was withdrawn over a period of 3 months, according to the treating physician's preference. In the case of an adverse

event that was not life-threatening, the treating physician had the option to decrease the daily dose of azathioprine by 25 to 50 mg or the weekly dose of methotrexate by 2.5 to 5 mg before deciding whether or not to discontinue the study drug.

During maintenance therapy, patients with fewer than 250 CD4+ T lymphocytes per milliliter continued to receive prophylaxis against *P. jirovecii* pneumonia; methotrexate recipients received this prophylaxis exclusively with aerosolized pentamidine. Patients who received methotrexate also received weekly oral folic acid (25 mg) or folic acid (5 mg), 48 hours after methotrexate intake, to prevent hematologic toxicity. After discontinuation of the maintenance immunosuppressive agents, trimethoprim-sulfamethoxazole (320 mg of trimethoprim plus 1600 mg of sulfamethoxazole per day) was recommended for 2 additional years for patients with Wegener's granulomatosis.¹⁴

EVALUATIONS

Patients were evaluated at diagnosis, at randomization, every 2 months thereafter for 1 year, and then every 6 months until the end of the study, when the last patient included in the study discontinued maintenance therapy. At each visit, disease activity was measured with the use of the original version of the Birmingham Vasculitis Activity Score (scores range from 0 to 63, with higher scores indicating more active disease).¹⁵ Routine biologic analyses included complete blood counts; measurements of serum creatinine, C-reactive protein, and aminotransferase; and analysis of the urinary sediment. ANCA testing was performed at diagnosis and, when possible, in patients who were initially positive for ANCA, at remission. Adverse events were graded on a scale of 1 to 4, according to World Health Organization (WHO) toxicity criteria,¹⁶ with grades 3 and 4 considered to be severe. Quality of life was assessed with the use of the 36-Item Short-Form General Health Survey (SF-36), which was filled out by patients at each visit. Scores on this scale range from 0 to 100, with higher scores indicating better health.¹⁷

STUDY END POINTS

The primary end point was defined as an adverse event causing death or leading to discontinuation of the study drug. These events could be due to allergy or intolerance, severe adverse events according to the physician's judgment, or events

that were not reversed after dose adjustment. Secondary end points were any adverse event or severe adverse event as determined by the treating physician, relapse, relapse-free survival, event-free survival (i.e., survival without relapse or discontinuation of the study drug because of an adverse event), and quality of life.

Remission was defined as a Birmingham Vasculitis Activity Score of 0 (i.e., the absence of signs of new or worsening disease activity). In a patient who had been in remission for more than 3 months, the diagnosis of relapse required the recurrence or the first appearance of one or more Birmingham Vasculitis Activity Score items attributable to active vasculitis.

STATISTICAL ANALYSIS

The sample size was calculated on the basis of the hypothesis that maintenance therapy with methotrexate, as compared with azathioprine, would result in a lower percentage of patients who discontinued the study drug or died because of an adverse event. For patients with Wegener's granulomatosis who received methotrexate, this rate was 6% after a median follow-up of 16 months, according to data from the National Institutes of Health.^{9,18} Such adverse events occurred in 24% of azathioprine recipients with rheumatoid arthritis, according to the data from the American Rheumatism Association Medical Information System,¹⁹ and in up to 46% of patients with

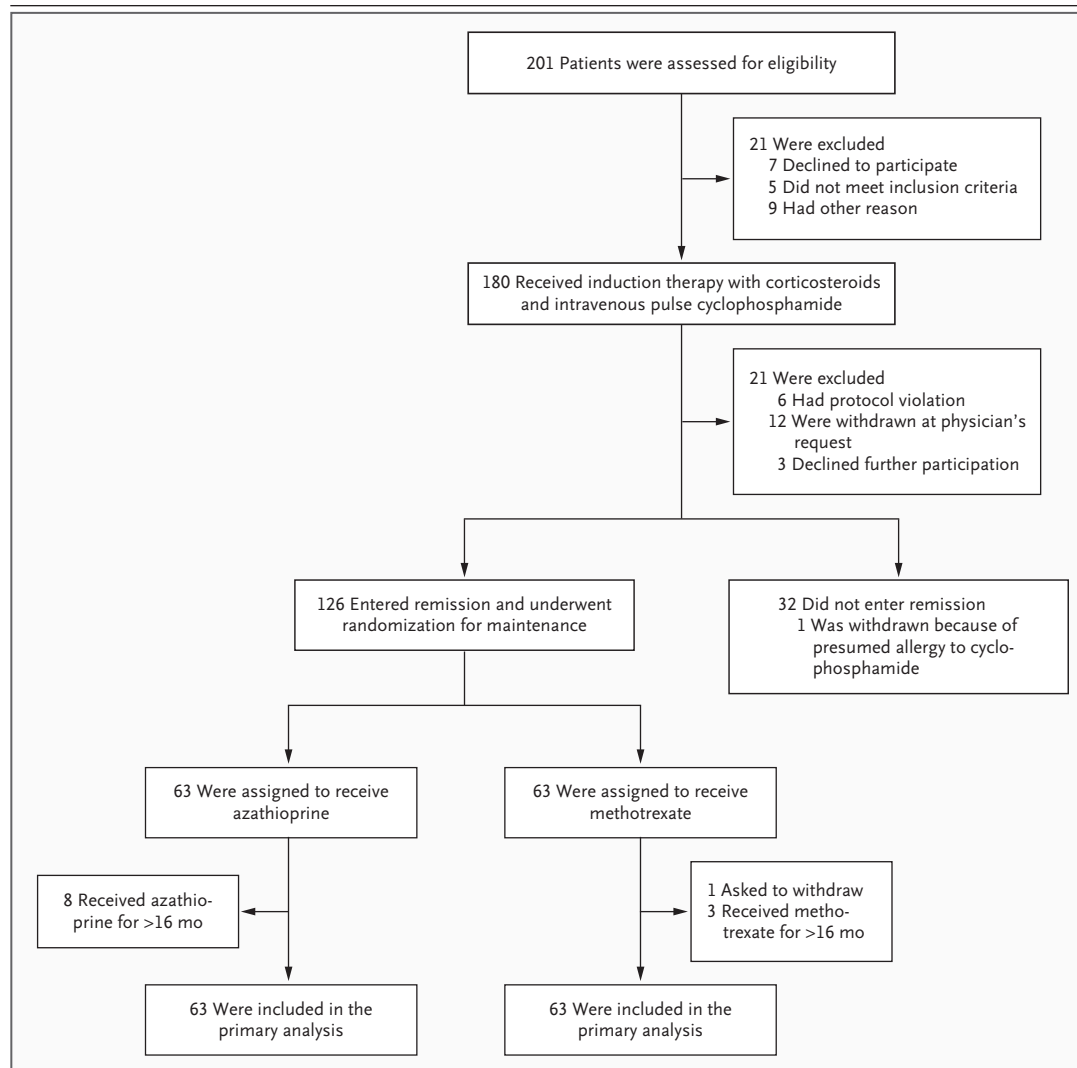


Figure 1. Enrollment, Randomization, and Inclusion in Primary Analysis.

Sjögren's syndrome.²⁰ On the basis of the hypothesis of a predicted rate of such adverse events of 30% among patients in the azathioprine group and 6% among patients in the methotrexate group, we calculated that 60 patients per treatment group were needed to achieve a significance level of 0.05 with a beta risk of 0.10. Assuming an estimated 5% rate of loss to follow-up or protocol deviation, the required number of patients for randomization was 126 (63 per group).

Table 1. Demographic and Clinical Characteristics of the Patients at Diagnosis and Randomization.*

Characteristic	Azathioprine Group (N=63)	Methotrexate Group (N=63)	P Value
Age at diagnosis — yr			
Mean	56.3±13.8	59.8±11.9	0.13
Range	21.6–79.2	25.2–78.6	
Sex — no. (%)			
Male	36 (57)	25 (40)	0.05
Female	27 (43)	38 (60)	0.05
Diagnosis — no. (%)			
Wegener's granulomatosis	48 (76)	48 (76)	1.00
Microscopic polyangiitis	15 (24)	15 (24)	1.00
Manifestations at diagnosis — no. (%)†			
Temperature >38.5°C (101.3°F)	40 (63)	33 (54)	0.29
Ear, nose, and throat involvement	47 (75)	47 (77)	0.75
Lung involvement	52 (83)	41 (67)	0.05
Alveolar hemorrhage	18 (29)	8 (13)	0.03
Nodules	30 (48)	25 (41)	0.46
Kidney involvement	47 (75)	48 (79)	0.59
Kidney involvement requiring dialysis	4 (6)	5 (8)	0.48
Nervous system involvement			
Peripheral	16 (25)	15 (25)	0.92
Central	7 (11)	2 (3)	0.07
Ocular involvement	19 (30)	14 (23)	0.36
Skin involvement	18 (29)	17 (28)	0.93
Cardiovascular system involvement	12 (19)	7 (11)	0.24
Gastrointestinal tract involvement	12 (19)	5 (8)	0.08
Birmingham Vasculitis Activity Score at diagnosis‡	23.6±7.5	21.2±7.1	0.07
Laboratory results			
Serum creatinine level — mg/dl			
At diagnosis	1.82±2.02	2.17±2.27	0.37
At randomization	1.52±1.15	1.4±0.61	0.56
Neutrophil count — cells/μl			
At diagnosis	8356±4186	8583±3400	0.75
At randomization	5534±2516	5412±2448	0.84
Lymphocyte count — cells/μl			
At diagnosis	1530±1106	1547±1058	0.94
At randomization	1273±414	1341±724	0.66
C-reactive protein level at diagnosis — mg/liter	104.8±81.7	90.6±66.3	0.31

Table 1. (Continued.)

Characteristic	Azathioprine Group (N=63)	Methotrexate Group (N=63)	P Value
ANCA-positive at diagnosis — no. (%)			
By immunofluorescence			
All	59 (94)	56 (89)	0.34
C-ANCA	44 (70)	36 (57)	0.14
P-ANCA	16 (25)	20 (32)	0.43
By ELISA			
All	58 (92)	55 (87)	0.38
PR3-ANCA	41 (65)	35 (56)	0.27
MPO-ANCA	18 (29)	21 (33)	0.56
ANCA-positive at randomization — no./no. tested among patients positive at diagnosis (%)§			
By immunofluorescence	22/44 (50)	15/43 (35)	0.15
By ELISA	16/44 (36)	7/39 (18)	0.06

* Plus-minus values are means \pm SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ANCA denotes antineutrophil cytoplasmic antibody, C-ANCA cytoplasmic ANCA-labeling pattern, ELISA enzyme-linked immunosorbent assay, MPO-ANCA antimitochondrial peroxidase ANCA (detected by means of ELISA), P-ANCA perinuclear ANCA-labeling pattern (detected by means of indirect immunofluorescence), and PR3-ANCA anti-proteinase 3 ANCA.

† Detailed clinical data at diagnosis were missing for two patients in the methotrexate group; their complete data at the time of randomization were available. Kidney involvement was defined as proteinuria ≥ 0.4 g of protein per 24 hours, hematuria $\geq ++$ with urinary dipstick, or ≥ 10 red cells per cubic millimeter, or serum creatinine level ≥ 125 μ mol per liter (1.41 mg per deciliter).

‡ The Birmingham Vasculitis Activity Score ranges from 0 to 63, with higher scores indicating more active disease.

§ The study protocol did not require ANCA testing at randomization. Results are expressed as the number of ANCA-positive patients among those who were positive at diagnosis and were tested at randomization.

Quantitative variables were compared with the use of Student's *t*-tests, and categorical variables were compared with the use of two-by-two tables or Fisher's exact tests. The primary end points, relapse-free survival and event-free survival, were compared with the use of Cox proportional-hazards models; times to these events were calculated from the start of maintenance therapy. Primary analyses were performed on an intention-to-treat basis. In addition, a per-protocol analysis, limited to the subjects who received treatment in full accordance with the study protocol, was conducted. All statistical tests were two-sided; *P* values of less than 0.05 were considered to indicate statistical significance. All analyses were performed with the use of SAS software, version 9.1.

RESULTS

ENROLLMENT AND CHARACTERISTICS OF THE PATIENTS

Between November 1998 and September 2003, a total of 201 patients were screened for eligibility

(Fig. 1). Thirty-two of the 159 eligible patients did not have a remission with the standardized induction regimen, and 1 patient had to discontinue cyclophosphamide because of a presumed allergy. The remaining 126 patients (79%) had a remission with the use of the study induction regimen and were randomly assigned to receive a study drug in one of two groups, with 63 patients per group. The last random assignment occurred in February 2004; the study was closed for analysis in February 2005.

Table 1 shows the characteristics of the patients at diagnosis and randomization. Among the 126 patients who underwent randomization, 96 (76%), equally distributed between treatment groups, had Wegener's granulomatosis. The diagnosis was histologically proved in 110 patients (87%); the remaining 16 patients had ANCA-positive disease.

Between diagnosis and randomization, the mean (\pm SD) creatinine level in patients who underwent randomization decreased significantly, from 175.8 ± 189.7 to 128.7 ± 78.5 μ mol per liter (1.99 ± 2.15 to 1.46 ± 0.89 mg per deciliter, *P*=0.03); this decrease was similar in both groups.

Table 2. Adverse Events after the Initiation of Assigned Maintenance Therapy.*				
Variable	All Patients (N = 126)	Azathioprine Group (N = 63) <i>no. of patients (%)</i>	Methotrexate Group (N = 63)	P Value
Cutaneous eruption				
Any	2 (2)	1 (2)	1 (2)	1.00
Severe	0	0	0	
Anemia†				
Any	4 (3)	2 (3)	2 (3)	1.00
Severe	1 (1)	0	1 (2)	1.00
Lymphopenia‡				
Any	24 (19)	10 (16)	14 (22)	0.36
Severe	4 (3)	1 (2)	3 (5)	0.62
Neutropenia§				
Any	5 (4)	2 (3)	3 (5)	1.00
Severe	3 (2)	0	3 (5)	0.24
Thrombopenia¶				
Any	4 (3)	1 (2)	3 (5)	0.62
Severe	1 (1)	0	1 (2)	1.00
Mucosal toxicity				
Any	7 (6)	0	7 (11)	0.01
Severe	4 (3)	0	4 (6)	0.12
Gastrointestinal event				
Any	19 (15)	8 (13)	11 (18)	0.46
Severe	0	0	0	
Liver toxicity				
Any	8 (6)	4 (6)	4 (6)	1.00
Severe	6 (5)	4 (6)	2 (3)	0.68
Infection				
Any	27 (21)	12 (19)	15 (24)	0.51
Severe	6 (5)	1 (2)	5 (8)	0.21
Cumulative no. of infections	46	19	25	
Respiratory event				
Any	4 (3)	1 (2)	3 (5)	0.62
Severe	2 (2)	0	2 (3)	0.50
Bone fracture				
Any	4 (3)	1 (2)	3 (5)	0.62
Severe	0	0	0	
Cystitis				
Any	0	0	0	
Psychiatric event				
Any	3 (2)	1 (2)	2 (3)	1.00
Severe	0	0	0	
Cancer	3 (2)	2 (3)	1 (2)	1.00

Table 2. (Continued.)

Variable	All Patients (N = 126)	Azathioprine Group (N = 63) <i>no. of patients (%)</i>	Methotrexate Group (N = 63)	P Value
Venous thrombotic event	3 (2)	1 (2)	2 (3)	1.00
Death due to study drug	1 (1)	0	1 (2)	1.00
Any adverse event				
Any	64 (51)	29 (46)	35 (56)	0.29
Severe	16 (13)	5 (8)	11 (18)	0.11
Requiring study-drug withdrawal or causing death	19 (15)	7 (11)	12 (19)	0.21

* Results are expressed as the number and percent of patients who had one or more adverse events as described, except for the cumulative number of infections reported. Severe adverse events correspond to grades 3 and 4 according to the toxicity criteria of the World Health Organization.¹⁶

† Anemia was defined as a hemoglobin level that was less than the lower limit of the normal value (i.e., 11 g per deciliter for women and 12 g per deciliter for men), and severe anemia was defined as a hemoglobin level that was less than 8 g per deciliter.

‡ Lymphopenia was defined as a total lymphocyte count that was less than 2000 cells per microliter, and severe lymphopenia was defined as a lymphocyte count that was less than 1000 cells per microliter.

§ Neutropenia was defined as a neutrophil count that was less than 2000 cells per microliter, and severe neutropenia was defined as a neutrophil count that was less than 1000 cells per microliter.

¶ Thrombopenia was defined as a platelet count that was less than 130,000 per microliter, and severe thrombopenia was defined as a platelet count that was less than 50,000 per microliter.

|| Liver toxicity was defined by an aminotransferase level (aspartate aminotransferase, alanine aminotransferase, or both) that was greater than twice the upper limit of the normal value, and severe liver toxicity was defined as an aminotransferase level that was greater than five times the upper limit of the normal value.

REMISSION-INDUCTION REGIMEN

The mean duration of induction therapy among the 126 patients who underwent randomization was 6.7±2.0 months, corresponding to a mean of 10.1±2.3 cyclophosphamide pulses and a mean cumulative cyclophosphamide dose of 10.4±3.3 g. The daily corticosteroid dose remained more than 20 mg for an average of 5.4±4.6 months, with a mean daily prednisone dose at randomization of 13.4±3.8 mg; the dose was similar in the two groups. Adverse events occurred during induction in 64 patients (51%), primarily the onset of diabetes (in 12 patients) and infections (in 17 patients).

STUDY END POINTS

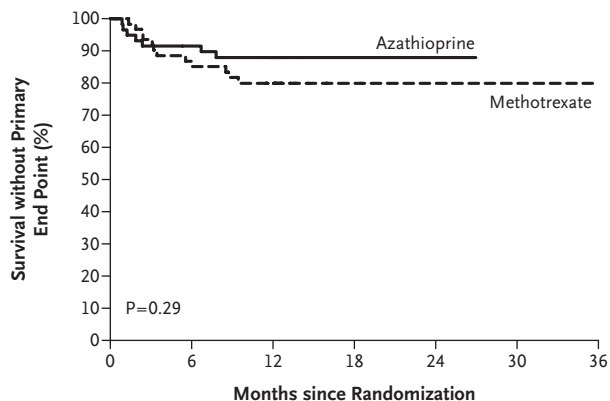
Adverse Events

After starting maintenance therapy, 29 azathioprine recipients had at least one adverse event as compared with 35 methotrexate recipients (46% vs. 56%, P=0.29) (Table 2). An adverse event led to immediate discontinuation of the study drug in five patients in the azathioprine group and seven patients in the methotrexate group. An adverse event led to discontinuation of the study drug because the adverse event was not reversed after a dose reduction in two patients who received azathioprine (with discontinuation due to hepa-

totoxicity) and four recipients of methotrexate (with discontinuation due to hepatotoxicity in two patients and pneumonitis due to drug hypersensitivity in two patients). One 75-year-old patient in the methotrexate group died of aplasia, complicated by septicemia, 2 months after starting maintenance therapy.

Overall, an adverse event leading to the primary end point (i.e., discontinuation of the study drug or death) occurred in 7 patients (11%) in the azathioprine group (because of hepatotoxicity in 4 patients and digestive intolerance within the first month after the initiation of treatment in 3 patients) and 12 patients (19%) in the methotrexate group (because of stomatitis, colitis, or both associated with cytopenia in 2 patients and not associated with cytopenia in 2 patients; pneumonitis in 3 patients; hepatotoxic effects in 2 patients; diffuse cutaneous eruption in 1 patient; and hematologic toxicity with sepsis in 2 patients and causing death in 1 of these patients) (P=0.21). The corresponding hazard ratio for methotrexate as compared with azathioprine was 1.65 (95% confidence interval [CI], 0.65 to 4.18; P=0.29) (Fig. 2A). The last measured creatinine level ranged from 54 to 292 μmol per liter (0.61 to 3.3 mg per deciliter) in these 7 azathioprine re-

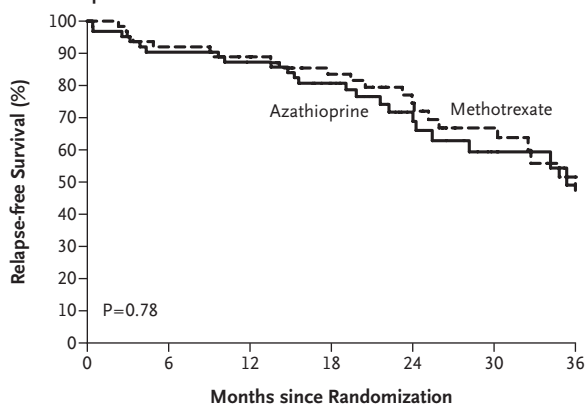
A Time to Adverse Event Leading to Study-Drug Discontinuation or Death



No. at Risk

Azathioprine	63	52	32	4	2	0	0
Methotrexate	63	51	30	3	1	1	1

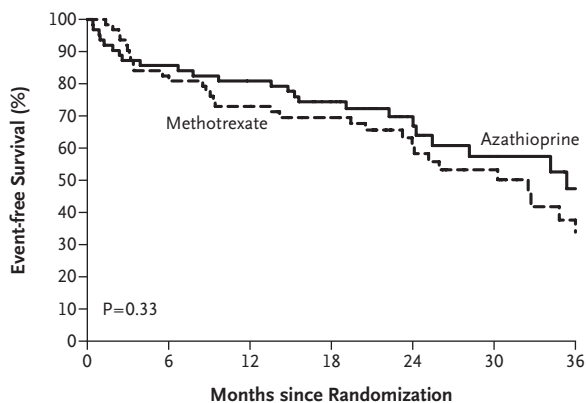
B Time to First Relapse



No. at Risk

Azathioprine	63	57	54	43	25	14	9
Methotrexate	63	58	53	44	30	22	11

C Time to First Event



No. at Risk

Azathioprine	63	54	50	39	24	14	9
Methotrexate	63	53	45	38	25	17	9

Figure 2. Kaplan–Meier Estimates of Outcomes.

Patients without any of the considered events were excluded at the date when maintenance treatment was discontinued (Panel A) or at the date of the last follow-up visit (Panels B and C). In Panel C, the first event was defined as the first relapse or adverse event leading to withdrawal of the study drug or causing death. The P values were calculated with the use of Cox proportional-hazards models.

ipients and from 66 to 251 μmol per liter (0.75 to 2.84 mg per deciliter) in these 12 methotrexate recipients (P=0.30).

Relapses

At the censoring date for analysis, the mean follow-up after randomization was 29.2 ± 13.3 months; this was similar in both groups (P=0.89). Twenty-three azathioprine recipients and 21 methotrexate recipients had a relapse (36% and 33%, respectively; P=0.71); all required further treatment with another immunosuppressant. The mean randomization-to-relapse interval was 20.6 ± 13.9 months; 32 of the 44 recorded relapses (73%) occurred after discontinuation of the study drug. The number of relapses per 100 patients per year was 15.1 in the azathioprine group and 13.6 in the methotrexate group.

Twenty-four months after randomization, relapse-free survival rates were 71.8% (95% CI, 59.7 to 83.8) in the azathioprine group and 74.5% (95% CI, 62.7 to 86.4) in the methotrexate group (Fig. 2B). The hazard ratio for the risk of relapse among methotrexate recipients as compared with azathioprine recipients was 0.92 (95% CI, 0.52 to 1.65; P=0.78). On the basis of these rates, the absolute risk reduction for relapse or death at 24 months in the methotrexate group was 1.9% (95% CI, -13.9 to 12.3).

Relapse rates and relapse-free survival rates 18 and 36 months after diagnosis are shown in Table 3 for our study and four other studies. The relapse-free survival rate in our study was slightly but not significantly higher among patients with microscopic polyangiitis than among patients with Wegener’s granulomatosis (hazard ratio, 0.51; 95% CI, 0.21 to 1.19; P=0.12).

Event-free Survival

The 24-month event-free survival rate was 69.9% (95% CI, 58.0 to 81.8) in the azathioprine group

Table 3. Studies Involving Patients with ANCA-Associated Vasculitides Who Received Corticosteroids and Cyclophosphamide Induction in a Staged-Treatment Strategy.*

Study	No. Patients†	Diagnosis	Maintenance Therapy	Follow-up from Diagnosis‡	Relapse-free Survival after Diagnosis	Relapse Rate§	Toxicity
WEGENT (ClinicalTrials.gov number, NCT00349674)	126	Newly diagnosed systemic Wegener's granulomatosis or microscopic polyangiitis with FFS ≥1	AZA vs. MTX for 12 mo	37.3±14.3 mo	At 18 mo: AZA 88.9% vs. MTX 90.5%	At 18 mo: AZA 17.8% vs. MTX 13.7%	Grade 3/4: AZA 7.9% vs. MTX 17.4%
CYCAZAREM ⁶	144	Newly diagnosed Wegener's granulomatosis, microscopic polyangiitis, or renal-limited vasculitis, with mild or moderate renal or other vital-organ involvement	Continued oral CYC vs. AZA	18 mo for all patients	At 36 mo: AZA 64.1% vs. MTX 69.0%	At 36 mo: AZA 50.1% vs. MTX 46.7%	Requiring drug withdrawal: AZA 11.1% vs. MTX 19.0%
WGENT ²¹ (ClinicalTrials.gov number, NCT0005007)	180	Newly diagnosed or relapsing Wegener's granulomatosis: limited (52 patients) or severe (118 patients) with BVAS ≥3¶	MTX or AZA (when serum creatinine level >2 mg/dl [177 μmol/liter]) alone, or combined with ETN¶¶	27 mo	At 18 mo: AZA 84.5% vs. CYC 86.3%	At 18 mo: AZA 15.5% vs. CYC 13.7%	Grade 1/2: AZA 41% vs. CYC 44%; grade 3/4: AZA 11% vs. CYC 10%
Langford et al. ⁹	42	Newly diagnosed or relapsing Wegener's granulomatosis	MTX for >2 yr	3 (range, 1–12) mo induction plus 32 mo (range, 5–71) maintenance		At 27 mo: MTX or AZA 32.8% vs. MTX or AZA plus ETN 30.6%	Grade 3/4 or death: MTX or AZA 57.1% vs. MTX or AZA plus ETN 56.2%
Sanders et al. ²²	136	Newly diagnosed or relapsing Wegener's granulomatosis or microscopic polyangiitis	Continued oral CYC vs. AZA (retrospective; total duration of therapy, 18–24 mo)	Up to 5 yr for some patients	At 18 mo: AZA 89.6% vs. CYC 88.1%	At 16 mo: 16%; at 32 mo: 52%	Requiring withdrawal of maintenance drug: 5%

* Plus-minus values are means ±SD. ANCA denotes antineutrophil cytoplasmic autoantibody, AZA azathioprine, BVAS Birmingham Vasculitis Activity Score, CYC cyclophosphamide, CYCAZAREM Cyclophosphamide versus Azathioprine as Remission Maintenance Therapy for ANCA-Associated Vasculitis, ETN etanercept, FFS five-factor score, MTX methotrexate, WEGENT Wegener's Granulomatosis–Entretien, and WGENT Wegener's Granulomatosis Etanercept Trial. Differences between treatment groups were not significant.

† ANCA-negative patients were eligible for enrollment in all these studies when vasculitis had been confirmed histologically.

‡ Follow-up was the mean duration from the start of induction therapy in patients with newly diagnosed disease or relapse in the WGET study and the studies by Langford et al.⁹ and Sanders et al.²² In the CYCAZAREM study, the censoring end point was 18 months after diagnosis in all patients. In the study by Langford et al.,⁹ the medians and range are given for the induction and maintenance phases. In the retrospective study of long-term outcomes by Sanders et al.,²² 45 of the 136 patients could be evaluated and were at risk for relapse 5 years after diagnosis.

§ Relapse rates were determined from the onset of induction therapy in patients with newly diagnosed disease or relapse and who entered remission with that regimen.

¶ WGET induction therapy consisted of combined corticosteroids and CYC in patients with severe Wegener's granulomatosis or MTX for patients with limited disease. MTX (or AZA when the serum creatinine level was >2 mg/dl) was the maintenance agent for 12 additional months in all patients who had a remission. ETN or placebo combined with induction therapy was started at the beginning of induction and prescribed for 12 months.

|| The total duration of therapy, as indicated, includes induction and maintenance regimens.

and 60.8% (95% CI, 47.9 to 73.7) in the methotrexate group (Fig. 2C). Among methotrexate recipients, the hazard ratio for an event was 1.30 (95% CI, 0.77 to 2.20; $P=0.33$).

Quality of Life

Physical and mental dimensions of the SF-36 scores for quality of life were improved at the end of the study, with 76.3±3.6% of the patients rating their health status as being “much better” or “somewhat better” than 1 year earlier. No significant difference was found between the treatment groups.

PER-PROTOCOL ANALYSIS

The per-protocol analysis excluded 12 patients (8 in the azathioprine group and 4 in the methotrexate group). In 11 patients, the administration of maintenance drug therapy exceeded 16 months, and 1 patient who received methotrexate withdrew from the study after 1 month because of the patient’s concern about a potential adverse event. No patient was lost to follow-up.

The hazard ratios for methotrexate as compared with azathioprine were 1.56 (95% CI, 0.61 to 3.97; $P=0.35$) for the primary end point, 0.75 (95% CI, 0.41 to 1.38; $P=0.36$) for relapse, and 1.11 (95% CI, 0.64 to 1.90; $P=0.72$) for an event (either an adverse event causing death or leading to discontinuation of the study drug, or relapse).

FOLLOW-UP

The total duration of corticosteroid therapy was 26.9±7.1 months (27±6.4 months in the azathioprine group and 26.7±7.8 months in the methotrexate groups, $P=0.86$). After discontinuation of the study drug, cancer was diagnosed in three patients (ovarian adenocarcinoma in one patient in the methotrexate group, and lung adenocarcinoma in one patient and breast carcinoma in one patient in the azathioprine group). Two patients who had discontinued the study drug because of an adverse event died during follow-up: one patient had discontinued methotrexate because of presumed immunoallergic pneumonitis and died 2 months later of *Pseudomonas aeruginosa* infection; the other stopped taking azathioprine after 3 months because of toxic hepatitis, switched to methotrexate, and died of a pulmonary embolism 7 months later. In addition, a patient who had a relapse while receiving methotrexate but had a remission with continuous oral cyclophosphamide died of sepsis 3 years later.

DISCUSSION

The aim of this trial was to determine the safety and efficacy of azathioprine versus methotrexate as maintenance therapy for Wegener’s granulomatosis and microscopic polyangiitis. The two drugs appeared to be similar alternatives for maintaining remission; however, our observations do not provide support for the working hypothesis that methotrexate would have a better toxicity profile than azathioprine. In fact, there was a trend in the opposite direction, especially for severe adverse events.

This study used a staged induction–maintenance strategy with corticosteroids and intravenous pulses of cyclophosphamide to achieve remission of Wegener’s granulomatosis and microscopic polyangiitis. According to data from several previous trials,^{3–5,23} intravenous cyclophosphamide is as effective as and less toxic than continuous oral administration of this drug for inducing remission of ANCA-associated vasculitides. After the present trial began, the results of the Cyclophosphamide versus Azathioprine as Remission Maintenance Therapy for ANCA-Associated Vasculitis (CYCAZAREM) trial⁶ indicated that oral cyclophosphamide induction allowed patients to switch successfully to azathioprine as soon as remission was attained. These results suggested that the three consolidating pulses of cyclophosphamide given to our patients between remission and the onset of maintenance therapy might now be considered unnecessary.

Although relapse was not the primary end point, our data suggest that neither study drug is more effective at maintaining remission in patients with Wegener’s granulomatosis or microscopic polyangiitis. Indeed, as reflected by the 95% confidence interval, comparing the two agents for absolute risk reduction (for relapse or death combined), the difference never exceeded 15% throughout 24 months after randomization.

Our study was powered to detect an absolute between-group difference of 24% for an adverse event leading to discontinuation of the study drug or death. The hazard ratio of 1.65 (95% CI, 0.65 to 4.18) for the risk of such an adverse event with methotrexate as compared with azathioprine raises the possibility that azathioprine might be safer, especially considering the small size of our patient population. Although the protocol provided the option to adjust the dose of the study drug

after an adverse event, one must also consider that each decision to discontinue the study drug may have been subjective. However, severe adverse events, classified according to the WHO,¹⁶ tended to occur more frequently in the methotrexate group, in which the only death related to the study drug occurred.

Low-dose methotrexate is considered to be relatively safe for the treatment of patients with rheumatoid arthritis.²⁴⁻²⁶ The somewhat higher rate of methotrexate-associated adverse events in our trial than the rates reported for rheumatoid arthritis is probably explained by the higher doses prescribed for patients with Wegener's granulomatosis or microscopic polyangiitis, many of whom also have impaired renal function. In the Nonrenal Wegener's Granulomatosis Treated Alternatively with Methotrexate (NORAM) trial,²⁷ among the 51 patients with nonrenal Wegener's granulomatosis who received methotrexate induction and maintenance therapy, adverse events led to the discontinuation of this drug in 8% of the patients. In another study, involving 42 patients with Wegener's granulomatosis,²⁸ hepatotoxicity developed in 24% of the patients, opportunistic infections developed in 9.5%, and pneumonitis developed in 7%. Given those results, even though we did not observe an association between the frequency and severity of adverse events and renal impairment in the methotrexate group, it seems wise to adjust the dose of the drug or to avoid its use in patients with severe renal impairment.

Logistic and financial considerations led to the open-label design of this study. Although the participation of numerous centers could also have introduced certain assessment biases, our observed rates of relapse and adverse events are

consistent with those previously reported separately for each drug in other studies of ANCA-associated vasculitis (Table 3).^{8,9,21,22}

Even though the induction-maintenance approach for treating Wegener's granulomatosis and microscopic polyangiitis probably represents an important therapeutic advance, high relapse rates persist. In the present and previous trials,^{4,6,9} immunosuppressive treatment was continued for at least 18 months after diagnosis, leaving unanswered the questions of the optimal duration of maintenance therapy and whether immunosuppression should be pursued for longer periods.²⁹ The identification of clinical variables, biologic variables, or both that are associated with an increased risk of relapse^{30,31} should lead to the development of risk-adapted strategies for improved maintenance treatment of ANCA-associated vasculitides.

In conclusion, neither drug appeared to maintain remission more effectively than the other. Thus, prioritizing safety issues seems reasonable, and the choice of one drug or the other might best be decided on the basis of each patient's individual situation.

Supported by a contract with Hospices Civils de Lyon (Délégation à la Recherche Clinique, Lyon, France, trial no. 97.129).

Preliminary results of this study were presented at the European League against Rheumatism Congress, Vienna, June 8-11, 2005; at the 12th International ANCA Workshop, Heidelberg, Germany, June 15-18, 2005; and at the American College of Rheumatology Scientific Meeting, San Diego, CA, November 12-17, 2005.

Dr. Mouthon reports receiving consulting and lecture fees from Actelion, Pfizer, and Laboratoire Français du Fractionnement et des Biotechnologies; and Dr. Cordier, lecture fees from GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

We thank Janet Jacobson for editorial assistance with an earlier version of the manuscript and Société Nationale Française de Médecine Interne for assistance with the recruitment of patients and investigators.

APPENDIX

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