

Randomized Trial of Cyclophosphamide Versus Methotrexate for Induction of Remission in Early Systemic Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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Objective. Standard therapy for antineutrophil cytoplasmic antibody–associated systemic vasculitis (AASV) with cyclophosphamide (CYC) and prednisolone is limited by toxicity. This unblinded, prospective, randomized, controlled trial was undertaken to determine whether methotrexate (MTX) could replace CYC in the early treatment of AASV.

Methods. Patients with newly diagnosed AASV, with serum creatinine levels <150 μ moles/liter, and without critical organ manifestations of disease were randomized to receive either standard oral CYC, 2 mg/kg/day or oral MTX, 20–25 mg/week; both groups

received the same prednisolone regimen. All drug treatments were gradually tapered and withdrawn by 12 months. Followup continued to 18 months. The primary end point was the remission rate at 6 months (noninferiority testing).

Results. One hundred patients were recruited from 26 European centers; 51 patients were randomized to the MTX group and 49 to the CYC group. At 6 months, the remission rate in patients treated with MTX (89.8%) was not inferior to that in patients treated with CYC (93.5%) ($P = 0.041$). In the MTX group, remission was delayed among patients with more extensive disease ($P = 0.04$) or pulmonary involvement ($P = 0.03$). Relapse rates at 18 months were 69.5% in the MTX group and 46.5% in the CYC group; the median time from remission to relapse was 13 months and 15 months, respectively ($P = 0.023$, log rank test). Two patients from each group died. Adverse events (mean 0.87 episodes/patient) included leukopenia, which was less frequent in the MTX versus the CYC group ($P = 0.012$), and liver dysfunction, which was more frequent in the MTX group ($P = 0.036$).

Conclusion. MTX can replace CYC for initial treatment of early AASV. The MTX regimen used in the present study was less effective for induction of remission in patients with extensive disease and pulmonary involvement and was associated with more relapses than the CYC regimen after termination of treatment. The high relapse rates in both treatment arms support the practice of continuation of immunosuppressive treatment beyond 12 months.

Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are the major categories of primary antineutrophil cytoplasmic antibody (ANCA)–

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associated systemic vasculitis (AASV), with an incidence of 20 cases/million people/year (1). They are characterized by necrotizing small vessel vasculitis and circulating antineutrophil cytoplasmic antibodies (ANCA) (2,3). Improved diagnostic procedures have enabled their earlier diagnosis and have improved awareness of these diseases (4).

At the time this trial was designed, the predominantly used treatment for induction of remission in AASV consisted of daily oral cyclophosphamide (CYC) plus corticosteroids (5). This empirical treatment leads to remission in ~90% of patients (6–8). However, it is associated with considerable long-term morbidity and even mortality (7,8). The aims of the European Vasculitis Study Group (EUVAS) are to standardize treatment, to subgroup patients at presentation according to disease stage, and to test alternative, safer treatments via randomized controlled trials (5,9). Single-center experience (10) has suggested that WG with normal or only moderately impaired renal function (creatinine <150 μ moles/liter) and without life-threatening disease manifestations (“early systemic disease”) can be successfully treated with weekly methotrexate (MTX). However, there has been no direct comparison with standard CYC. The long-term tolerability of MTX has been demonstrated in the treatment of rheumatoid arthritis (11). This unblinded, prospective, randomized, controlled trial evaluated whether MTX is comparable with CYC for induction of remission in early AASV.

PATIENTS AND METHODS

Noninferiority of MTX versus CYC was assessed, assuming a remission rate of 92% with CYC at 6 months, and accepting a difference in efficacy of 15% with a power of 0.8 and a 1-sided Type I error of 0.05, which necessitated a sample size of at least 92 patients (nQuery Advisor, version 5.0; Statistical Solutions, Cork, Ireland). The study was conducted according to the Declaration of Helsinki, and approval of ethics was obtained from each participating center. Participating physicians are listed in Appendix A.

Study design. After informed consent was obtained, patients were randomized at entry to receive either the “consensus standard regimen” of CYC plus prednisolone for 12 months or the “best alternative regimen” consisting of MTX plus prednisolone (5). All drugs were tapered and withdrawn by 12 months, while followup continued to 18 months from entry.

Eligibility criteria. To be included in the study, patients had to have a new diagnosis of WG or MPA, with involvement of 1 or more organ systems compatible with WG or MPA, together with constitutional symptoms (2 or more of the following symptoms: fever, headaches, myalgia, arthralgia, fatigue, weight loss >2 kg/week, anorexia after exclusion of

another multisystem disease, systemic infection, or a malignant condition). Additional inclusion criteria were elevated erythrocyte sedimentation rate (ESR) (>45 mm/hour) and/or a C-reactive protein (CRP) level greater than twice the upper limit of normal values (indicating systemic disease), or ANCA positivity (cytoplasmic ANCA [cANCA] pattern by indirect immunofluorescence or positivity for proteinase 3 [PR3] or myeloperoxidase [MPO] by enzyme-linked immunosorbent assay [ELISA], as defined by the protocol), or a nonrenal biopsy demonstrating an inflammatory infiltrate dominated by neutrophils in conjunction with either giant cells and/or epithelioid granuloma and/or small vessel necrotizing vasculitis (12–14).

Exclusion criteria were as follows: 1) organ or life-threatening manifestations (severe hemoptysis associated with bilateral infiltrates, cerebral infarction due to vasculitis, rapidly progressive neuropathy, orbital pseudotumor, massive gastrointestinal bleeding, heart failure due to pericarditis or myocarditis), 2) creatinine >150 μ moles/liter, urinary red cell casts, or proteinuria >1.0 gm/day, 3) skin vasculitis only, 4) coexistence of another multisystem autoimmune disorder, 5) malignancy, 6) replicative hepatitis B infection or known human immunodeficiency virus positivity, or 7) age <18 or >75 years.

Drug regimens. The MTX group received oral MTX 15 mg/week escalating to a maximum of 20–25 mg/week by 12 weeks, which was then maintained until month 10 and then tapered and discontinued by month 12. The CYC group received daily oral CYC 2 mg/kg/day (maximum 150 mg/day) until remission, for a minimum of 3 and a maximum of 6 months. The CYC dosage was reduced by 25 mg/day in patients age >60 years and was withdrawn if the total white blood cell count fell below 4×10^9 /liter. At remission, CYC was reduced to 1.5 mg/kg/day until month 10, when it was tapered and discontinued by month 12. Both treatment groups received oral prednisolone 1 mg/kg/day, tapered to 15 mg/day at 12 weeks and 7.5 mg/day by 6 months, and discontinued by 12 months. Prophylaxis against steroid-induced gastritis, fungal infection, *Pneumocystis jiroveci* (PCP) pneumonia, and osteoporosis was optional.

Definitions and guidelines. Disease definitions were in accordance with those issued by the 1992 Chapel Hill Consensus Conference (14) and previous reports from this group (9,12).

Using the list of 64 predefined items from the Birmingham Vasculitis Activity Score (BVAS) (15), remission was defined as the absence of new or worse clinical disease activity (BVAS 1) but allowed persistent activity (BVAS 2) in 1 item scoring <2 points. Relapse was defined on the basis of clinical manifestations, and only if remission was previously achieved. Major relapse was defined as recurrence or new onset of vasculitis activity that threatened the function of vital organs (e.g., lung, kidney, brain, motor nerve, or eye). Minor relapse was defined as the reemergence of disease activity, sufficient to warrant an increased prednisolone dose, yet without organ or life-threatening manifestations. Remission and relapse determinations were made by the local investigator.

Blood counts were checked weekly for the first month, twice weekly for the second month, and monthly thereafter. A leukocyte count < 4×10^9 /liter was defined as leukopenia, with < 1.5×10^9 /liter defined as severe leukopenia. If leukopenia occurred, CYC was withheld until the leukocyte count was

Table 1. Demographic data on actively treated patients, by randomization group*

	MTX (n = 49)	CYC (n = 46)	All (n = 95)
Age, median (range) years	48.8 (18–72)	53.5 (22–78)	53 (18–78)
Female/male	25/24 (51/49)	26/20 (57/43)	51/44 (54/46)
WG	46 (94)	43 (93)	89 (94)
MPA	3 (6)	3 (7)	6 (6)
cANCA	41 (84)	35 (76)	76 (80)
pANCA	4 (8)	6 (13)	10 (11)
PR3 ANCA positive	37 (76)	33 (72)	70 (74)
MPO ANCA positive	5 (11)	7 (15)	12 (13)
Histologic confirmation of WG/MPA	30 (65)	21 (46)	51 (55)
Positive sinus imaging	41/47 (87)	37 (80)	78/93 (84)
Serum creatinine level at entry, median (range) μ moles/liter	84.5 (44–126)	84.5 (42–149)	84.5 (42–149)
Microhematuria at entry	13 (27)	14 (30)	27 (28)
C-reactive protein level at entry, median (range) mg/liter	57 (1–288)	46 (1–332)	46 (1–332)
Erythrocyte sedimentation rate at entry, median (range) mm/hour	73 (5–110)	65.5 (10–120)	66 (5–120)
DEI at entry, median (range)	11 (7–19)	9 (3–17)	11 (3–19)
BVAS at entry, median (range)	15 (2–40)	15 (4–30)	15 (2–40)
VDI at entry, median (range)	1 (0–6)	0 (0–8)	0 (0–8)

* Except where indicated otherwise, values are the number (%). MTX = methotrexate; CYC = cyclophosphamide; WG = Wegener's granulomatosis; MPA = microscopic polyangiitis; cANCA = cytoplasmic antineutrophil cytoplasmic antibody; pANCA = perinuclear ANCA; PR3 = proteinase 3; MPO = myeloperoxidase; DEI = Disease Extent Index; BVAS = Birmingham Vasculitis Index; VDI = Vasculitis Damage Index.

$>4 \times 10^9$ /liter, and was then recommenced with the dosage reduced by 25 mg/day. In the MTX group, folic/foinic acid was administered in cases of elevation of transaminase levels, leukopenia $<3 \times 10^9$ /liter, or thrombocytopenia $<100 \times 10^9$ /liter.

Evaluations. Study assessments were performed at entry, then monthly for the first 6 months, once every 3 months thereafter, and at relapse. Assessments included complete blood count, measurements of ESR, CRP, serum creatinine, alanine transaminase, alkaline phosphatase, albumin, and glucose, dipstick urinalysis, urine microscopy, and nasal swab. The following validated clinical outcome measures were scored at every visit, as described previously (16): BVAS, Disease Extent Index (DEI) (17), and the Short-Form 36 functional questionnaire (SF-36) (18). Cumulative damage (Vasculitis Damage Index) [VDI] (19) from any cause since disease onset was scored at entry and every 6 months thereafter. Creatinine clearance and ANCA studies and chest and sinus radiography were performed at entry. Adverse events were graded for severity by predefined criteria, and their relationship to trial medication was scored.

Randomization and statistical analysis. Randomization was performed centrally in blocks of 4 by country, with stratification by diagnosis (WG or MPA). Primary data were collected at the participating centers into trial record books. After checking, they were entered into a central database. The data were analyzed using the SPSS statistical software package (version 11; Chicago, IL).

The primary end point was induction of remission within 6 months. The remission rates were compared by noninferiority testing of the one-sided 95% confidence interval (95% CI) for the difference of relative frequencies (StatXact-5; Cytel Software, Cambridge, MA) on an intention-to-treat basis, with death, study withdrawal, or loss to followup regarded as treatment failure. Time to remission was compared between groups by log rank test. Demographic details (Table 1) were compared

between groups by chi-square test for categorical variables and Mann-Whitney U test for continuous variables. The effect of demographic and disease variables on remission at 6 months was assessed by chi-square test for categorical variables and the Mann-Whitney U test for continuous variables, and the effect on time to remission was assessed by log rank test and Cox proportional hazards analysis.

Time to disease relapse and adverse effects were secondary end points. Time from remission to relapse was compared by log rank test. The effects of demographic and disease variables on time to remission and disease-free survival were assessed by log rank test for categorical variables and by Cox proportional hazards analysis for continuous variables. The number of patients with mild-to-moderate or severe-to-life-threatening adverse events were compared between groups by 2×2 contingency tables and Fisher's exact test.

The surrogate end points were the BVAS, DEI, VDI, SF-36, CRP level, ESR, leukocyte counts, and cumulative prednisolone dose. Differences in BVAS (1 and 2), VDI, laboratory values at each evaluation, and cumulative prednisolone doses between groups were assessed by Mann-Whitney U test. At entry, all items of disease activity were classified as BVAS 1 items denoting new or worse disease activity. Thereafter, activity persisting for longer than 1 month was classified as BVAS 2 items, reflecting persistent "grumbling" disease. Mean SF-36 scores were calculated for each of the 8 dimensions, using the Likert method of summated ratings, and change in scores over time was compared between groups by repeated-measures analysis.

RESULTS

Patients. One hundred patients were registered from 26 centers in 10 European countries between July 1995 and September 2000. Of these 100 patients, 51

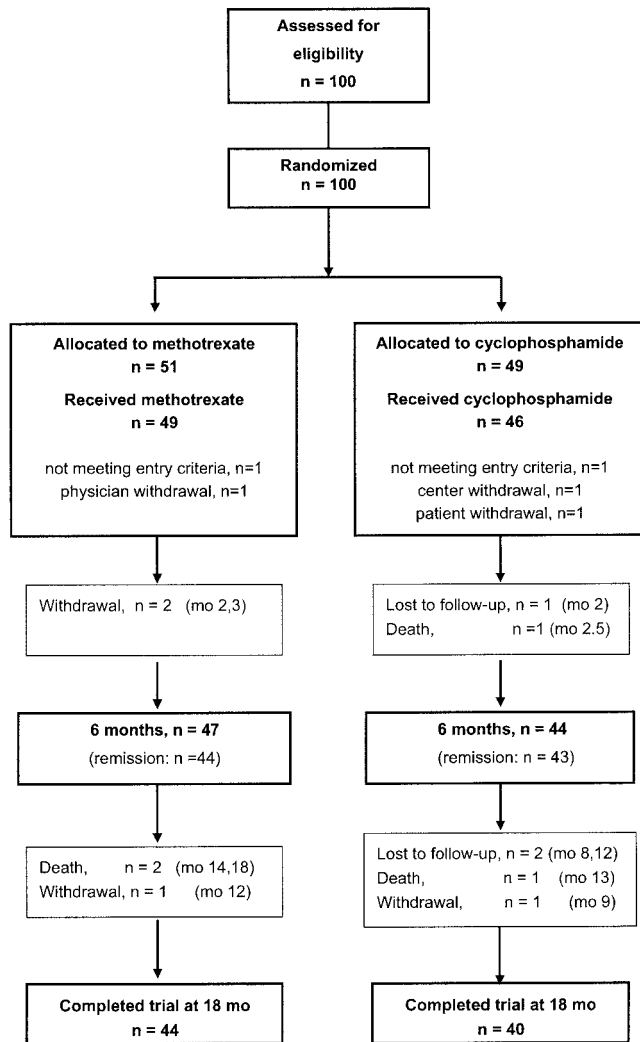


Figure 1. Distribution of patients in the 18-month trial.

were randomized to the MTX group and 49 to the CYC group (Figure 1). After randomization, 2 patients from the MTX group and 3 from the CYC group withdrew before starting treatment: 1 patient had tuberculosis (MTX group, did not meet entry criteria), 1 had deteriorating renal function (CYC group, did not meet entry criteria), 1 patient withdrew consent (CYC group), 1 treating center withdrew (CYC group), and 1 patient was withdrawn by the physician (MTX group) (Figure 1). Among the 95 actively treated patients, there were no statistically significant differences in demographic, clinical, or laboratory features at entry (Table 1 and Figure 2a). Eighty-nine patients had WG and 6 had MPA. There was histologic confirmation of WG/MPA in 55%

of patients (Table 1), and ANCA was positive by indirect immunofluorescence or ELISA in 93% of patients.

Withdrawals. Three patients were lost to follow-up from the CYC group, at 2, 8, and 12 months, respectively. Another patient was withdrawn from the CYC group at 9 months due to cardiopulmonary failure. Three patients were withdrawn from the MTX group, at 2, 3, and 12 months, due to primary treatment failure, congestive heart failure, and relapse, respectively (Figure 1).

Treatment protocol violations. In the MTX group, 2 patients switched from MTX to CYC at 2 months. Two stopped MTX treatment prematurely (though after having achieved remission) at 3.5 and 4.5

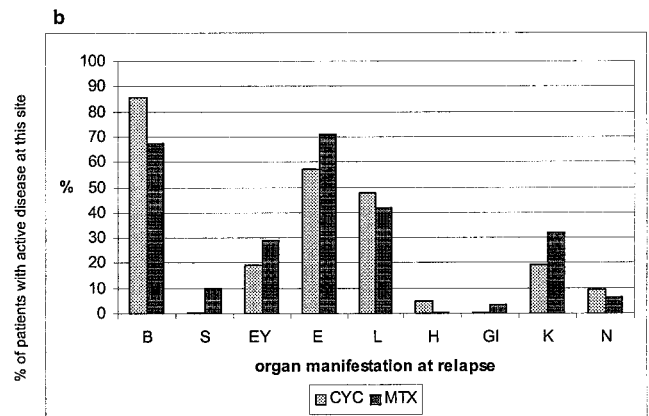
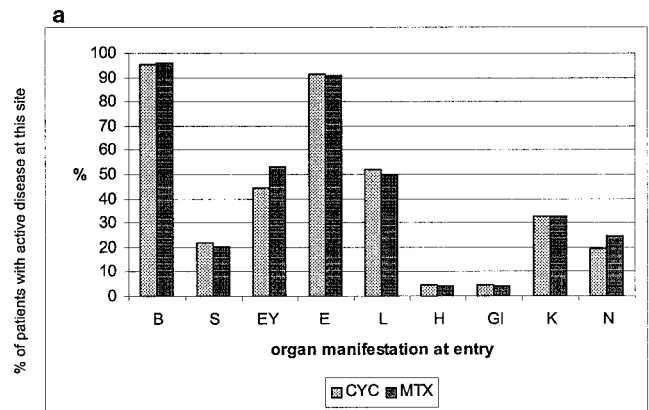


Figure 2. Distribution of organ manifestations at entry (a) and relapse (b), according to the Disease Extent Index. B = constitutional symptoms, including arthralgia/arthritis; S = skin; EY = eye; E = ears, nose, throat; L = lung; H = heart; GI = gastrointestinal; K = kidney; N = nervous system; CYC = cyclophosphamide; MTX = methotrexate.

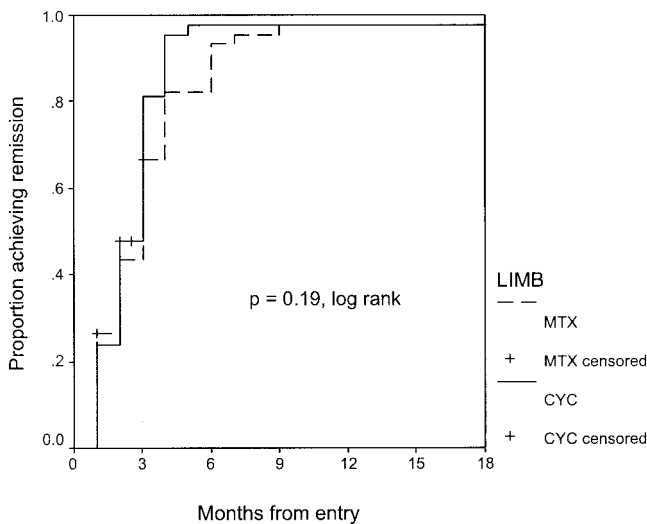


Figure 3. Time to remission (Kaplan-Meier curve) in the methotrexate (MTX) and cyclophosphamide (CYC) groups.

months because of liver dysfunction. Two continued to receive MTX beyond month 12, due to persistent disease activity. In the CYC group, the CYC dosage was increased in 1 patient because of unsatisfactory disease control and 1 patient was switched to azathioprine at 5 months due to mild lymphopenia, anemia, and the concurrent wish not to continue CYC treatment. Another patient from the CYC group was switched to MTX at 4 months, after recurrent leukopenia with CYC. The latter 2 patients had achieved remission at the time of CYC cessation.

Remissions. Within 6 months of the initiation of therapy, remission was achieved in 44 of 49 MTX-treated patients (89.8%), as compared with 43 of 46 CYC-treated patients (93.5%). Thus, the null hypothesis of inferiority by more than 15% was rejected ($P = 0.041$). Two further patients in the MTX group subsequently achieved remission at 7 and 9 months (Figure 3). No demographic or disease variables at entry were significantly associated with remission. The median time to remission was 3 months (range 1–9) in the MTX group and 2 months (range 1–5) in the CYC group ($P = 0.28$) (hazard ratio for MTX versus CYC 0.80 by log rank test [95% CI 0.52–1.22]). However, time to remission in the MTX group was significantly longer than that in the CYC group among the patients whose entry DEI was above the median of 10 ($P = 0.04$) and those with lower respiratory tract involvement (nodules and/or cavities and/or pulmonary infiltrates) ($P = 0.03$). The BVAS 1 score at entry correlated with time to remission ($P = 0.014$) in both treatment groups, whereas there

were no correlations with age, sex, disease duration before entry, or the following disease variables at entry: white blood cell count, CRP level, ANCA titer, presence of vasculitis or neutrophil infiltrate on histologic analysis, or urinary red blood cells.

Deaths. There were 4 deaths in the 2 study groups. In the MTX group, there was 1 death from a presumed cardiac event, following a major relapse at 14 months, and 1 death from pancreatic carcinoma at 18 months. Both patients had achieved remission. In the CYC group, 1 death was due to cytomegalovirus pneumonia at 2.5 months; the patient's lymphocyte count at this time was 0.2×10^9 /liter. The other death (at 13 months) was due to preexisting idiopathic pulmonary fibrosis.

Relapses. Of the patients in whom remission was achieved during the treatment period, 32 of 46 in the MTX group (69.5%) had a relapse, as compared to 20 of 43 in the CYC group (46.5%). Time to relapse from remission was longer in the CYC group than in the MTX group ($P = 0.023$), as shown in Figure 4 (median 13 months [range 2–17] in the MTX group, and 15 months [range 4–17] in the CYC group) (hazard ratio for MTX versus CYC 1.85 [95% CI 1.06–3.25]). In the MTX group there were 14 major and 18 minor relapses; of the latter, 3 were followed by major relapses. In the CYC group there were 9 major and 11 minor relapses. Organ manifestations at relapse were evenly distributed between groups (Figure 2b), and occurred predominantly

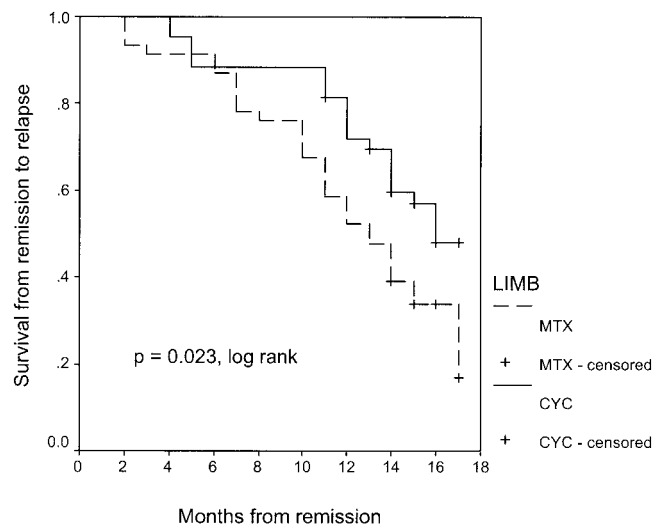


Figure 4. Time to first relapse from remission (Kaplan-Meier curve) in the methotrexate (MTX) and cyclophosphamide (CYC) groups. Patients who did not achieve remission within the first 12 months are excluded.

Table 2. Adverse events by type and treatment group*

Type of adverse event	Mild/moderate		Drug cessation, MTX/CYC	Severe/ life-threatening		Drug cessation, MTX/CYC
	MTX	CYC		MTX	CYC	
Allergy	–	–		1	–	
Thrombocytopenia	–	1		–	–	
Infection	5	5	1/0	4	4	0/1
Leukopenia	3	14	0/1	1	–	1/0
Multiple leukopenia	–	6		–	–	
Alopecia	–	1		–	–	
Cataract	–	1		–	–	
Osteoporosis	–	–		–	1	
Avascular necrosis	–	–		1	–	
Diabetes	–	3		–	–	
Infertility	–	–		1	–	
Hypertension	3	1		–	–	
Liver dysfunction	7	1	2/0	–	–	
Nausea/vomiting	1	–		–	–	
Hypersensitivity reaction	–	1	0/1	–	–	
Other	10	5		1	1	
Total	29	39	3/2	9	6	1/1

* MTX = methotrexate; CYC = cyclophosphamide.

in the respiratory tract. There were no significant associations between disease-free survival and demographic or disease variables at entry.

Laboratory features. There were no significant differences in sequential values of CRP, ESR, or creatinine between groups. Total white blood cell, neutrophil, and lymphocyte counts were lower in the CYC than in the MTX groups from 1 month to 15 months ($P < 0.01$).

Adverse events. Eighty-three adverse events occurred in 51 of 95 treated patients (mean 0.87 episodes/patient); 68 were mild or moderate and 15 severe or life-threatening (Table 2). Leukopenia was more common in the CYC group ($P = 0.012$) and liver dysfunction more common in the MTX group ($P = 0.036$). The relationship of adverse events to the study medication was rated as highly probable in 74% of the events in the CYC group but only in 34% of the events in the MTX group. Severe or life-threatening infections consisted of 1 fatal case of cytomegalovirus pneumonitis, 1 case of *Staphylococcus aureus*-induced gonarthrititis, and 2 episodes of *Corynebacterium* infection (in 1 patient) in the CYC group; in the MTX group, there were 2 cases of pneumonia, 1 urinary tract infection, and 1 unspecified infection. At the time of infection, none of these patients had received PCP pneumonia prophylaxis or antibiotics, and their white blood cell count was normal; 4 patients had mild lymphopenia, including the 1 with the cytomegalovirus infection.

Cumulative steroid dose. The median cumulative prednisolone dose was higher in the MTX group (8.8 gm

[interquartile range 6.3–11.1]) than in the CYC group (6.2 gm [interquartile range 5.4–7.9]) ($P = 0.001$). Doses were similar for the first 6 months; major differences in dosage occurred only after month 12. At 18 months, patients with pulmonary involvement had received a significantly higher cumulative prednisolone dose than those without, irrespective of their treatment group.

BVAS, VDI, and SF-36. BVAS 1 scores, representing new or worse disease activity, fell rapidly within the first 3 months, and BVAS 2, representing persistent grumbling disease activity, decreased more slowly, both without significant differences between the groups at any time point. Irreversible damage was present in some patients at entry, reflecting previous disease activity. VDI scores, representing any damage and/or disease activity present for >3 months, increased throughout the trial from a median of 0 (range 0–7) at study entry to 2 (range 0–8) at 18 months, without differences between groups. The SF-36 functional scores were depressed at entry for all 8 dimensions and increased by 6 months ($P < 0.01$). However, throughout the trial, scores persisted below control values. There were no differences between groups.

DISCUSSION

This randomized controlled trial was designed to examine whether patients could be spared the toxicity from standard CYC treatment by the alternative use of MTX for remission induction in early AASV without

critical disease manifestations. Patients were randomized to receive either consensus standard therapy with CYC or MTX therapy. The results of this trial demonstrated the clinically equivalent efficacy of MTX and CYC with regard to remission rates within 6 months of treatment. Thus, MTX is an appropriate alternative to CYC for obtaining remission in patients with early AASV, with the potential to avoid CYC exposure and its long-term consequences.

The remission rate with MTX in our cohort is higher than that reported in previous uncontrolled studies in which MTX was used for induction of remission in WG (30 of 41 patients [71%] [20], 10 of 17 patients [59%] [21], 14 of 19 patients [74%] [22]). However, the patient cohorts are not entirely comparable, since 2 of the former studies (20,21) also included patients with progressive disease despite other immunosuppressive treatment or patients with previous relapses, and 1 study used a much lower concomitant prednisolone dosage (21). Alternatively, a long-term substudy (23) of 1 of the studies (20), analyzing only the patients with active glomerulonephritis and serum creatinine levels ≤ 2.5 mg/dl, showed achievement of renal remission in all 20 patients. The differing diagnostic and disease status definitions, eligibility criteria, and variable treatment regimens make comparison of these studies difficult and may account for the differences in remission rates.

The correlation of time to remission with disease activity (BVAS 1) and the observation that the time to remission was longer in the MTX group than in those with more serious disease or those with lower respiratory tract disease at presentation is important. This suggests that MTX, at least with the regimen used in this study, is likely to be less effective than CYC for patients with more extensive disease. The incremental dosing of MTX during the first 12 weeks in the trial, as used in previous studies (7,22), may have contributed to the slower response. The patient subgroups that fared less well when treated with MTX in this trial may benefit from either higher initial MTX doses, parenteral instead of oral administration of MTX, or alternative therapy, especially because patients with pulmonary involvement at diagnosis have been shown to have a higher mortality rate than those without (8).

The observed relapse rates of 69.5% and 46.5% in the MTX and CYC groups at 18 months were higher than in previous reports on these agents (7,20,23–27). While this may have reflected differences in extent and duration of disease, it may also be the result of early cessation of immunosuppression at 12 months. Indeed, the rate of relapses before 12 months in this study was

similar to that observed in a previous study by our group, involving patients with generalized vasculitis with more severe organ manifestations, in whom immunosuppression was continued for 18 months. In that study, a relapse rate of 14% at 18 months was demonstrated in the CYC-treated patients (16). Most relapses in our study occurred after treatment withdrawal at 12 months, which corresponds to a previous report in which 79% of the observed relapses occurred after either reduction or discontinuation of MTX (20). After withdrawal of the drug the immunosuppressive effect of MTX was not sustained, as reflected by the significantly shorter median time from remission to relapse in the MTX group as compared with the CYC group (13 versus 15 months). Experience shows that a substantial proportion of relapses after reduction or cessation of MTX can be successfully treated with MTX again (20,22,23). In our trial, the higher relapse rate in the MTX group compared with the CYC group was reflected by a higher cumulative prednisolone dose, but not by a higher damage score (VDI) in the MTX group at study end.

The decision to stop treatment at 12 months was a group decision by consensus, because at the time of the trial design, longer exposure to CYC was not believed to be justified in this patient subgroup, given the well-known serious treatment-related morbidity and mortality (7,28). At that time, outcome data adapted to different disease stages did not exist, and there was information on a surprisingly high rate of survival in patients who had never been treated at all or had been treated with corticosteroids alone (28).

In addition to different treatment regimens, the vasculitic disease entity by itself may have an important impact on the relapse rate. The patients in the present trial were almost exclusively diagnosed as having WG, with the majority of cases associated with cANCA positivity. Recently, a higher relapse rate in WG compared with MPA in PR3 cANCA-positive disease has been reported with MPO pANCA-positive disease has been reported by several groups (16,29,30).

In the present trial, the subgroup of patients with early AASV and PR3 cANCA-positive WG, but without significant kidney involvement was more difficult to treat than anticipated. In view of the high relapse rates in these patients after MTX or CYC withdrawal, this study unequivocally demonstrates the need for continued immunosuppression with either an immunosuppressive drug plus corticosteroids or low-dose corticosteroids alone, beyond the 12-month treatment point for this subgroup.

There were significantly higher incidences of liver

dysfunction in the MTX group and of leukopenia in the CYC group; other adverse effects were evenly distributed between groups and were mostly of mild-to-moderate severity (Table 2). The rate of increases in transaminase levels in the MTX group could possibly have been reduced by routine prophylactic folic/folinic acid supplementation in every patient, irrespective of the occurrence of adverse events, as is current practice today.

There was no significant difference in the incidence of infections of all grades of severity for either group. Since most infections occurred during the remission induction phase, it is likely that the concomitant treatment with high-dose prednisolone during induction of remission was a contributing factor. A case of cytomegalovirus pneumonitis in the CYC group was the only treatment-related fatality. No MTX-induced pneumonitis was observed. PCP prophylaxis was not used in this study, because the previous incidence of PCP was low among the participating centers. Since trimethoprim/sulfamethoxazole (TMP/SMX), the standard prophylactic agent for PCP, has been described to be effective in WG by itself, it was agreed not to use TMP/SMX in the present study. In view of the high cost of the alternative drug, inhaled pentamidine, there was no consensus on routine administration of this agent. Prophylaxis against osteoporosis with vitamin D and calcium was recommended; there is now more recent evidence supporting the routine use of a bisphosphonate for this indication.

In conclusion, this study has shown that CYC exposure can be reduced or even avoided in early AASV, mainly in cases of WG, by administering MTX from the time of diagnosis. Subgroup analysis suggests that the MTX regimen used in this study is less effective for induction of remission in patients with pulmonary involvement or more extensive disease, when a higher initial MTX dosage or alternative or additional therapies may be required. Maintenance of remission was unsatisfactory in both groups, with a significantly higher relapse rate and shorter time from remission to relapse in the MTX as compared with the CYC group, suggesting that remission maintenance therapy in patients with early AASV should be continued beyond 12 months.

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