TRIMETHOPRIM–SULFAMETHOXAZOLE (CO-TRIMOXAZOLE) FOR THE PREVENTION OF RELAPSES OF WEGENER'S GRANULOMATOSIS

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ABSTRACT

Background Respiratory tract infections may trigger relapses in patients with Wegener's granulomatosis in remission. Uncontrolled data have suggested that treatment with trimethoprim–sulfamethoxazole (co-trimoxazole) may be beneficial.

Methods We conducted a prospective, randomized, placebo-controlled study of the efficacy of co-trimoxazole (800 mg of sulfamethoxazole and 160 mg of trimethoprim) given twice daily for 24 months in preventing relapses in patients with Wegener's granulomatosis in remission during or after treatment with cyclophosphamide and prednisolone. Relapses and infections were assessed with predefined criteria based on clinical, laboratory, and histopathological findings. Patients were evaluated at least once every three months for signs of disease activity, compliance with the treatment regimen, side effects of the therapy, and evidence of infections. Titers of serum antineutrophil cytoplasmic antibodies were measured serially.

Results Forty-one patients were assigned to receive co-trimoxazole, and 40 to receive placebo. In 8 of the 41 patients in the co-trimoxazole group (20 percent), the drug had to be stopped because of side effects. According to life-table analysis, 82 percent of the patients in the co-trimoxazole group remained in remission at 24 months, as compared with 60 percent of those in the placebo group (relative risk of relapse, 0.40; 95 percent confidence interval, 0.17 to 0.98). There were fewer respiratory tract infections ($P = 0.005$) and non–respiratory tract infections ($P = 0.05$) in the co-trimoxazole group than in the placebo group. There were no significant differences in antineutrophil cytoplasmic antibody titers at any time. Proportional-hazards regression analysis identified treatment with co-trimoxazole as an independent factor associated with prolonged disease-free survival and a positive antineutrophil cytoplasmic antibody test at the start of treatment as a risk factor for relapse.

Conclusions Treatment with co-trimoxazole reduces the incidence of relapses in patients with Wegener's granulomatosis in remission. (N Engl J Med 1996;335:16-20.)

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WEGENER'S granulomatosis is a disease of presumed autoimmune origin characterized by necrotizing granulomatous inflammation of the upper and lower airways and necrotizing vasculitis that is especially likely to involve the kidneys.[1] In untreated patients, the mean survival is only five months and the one-year mortality rate is 82 percent.[2] Treatment with cyclophosphamide and prednisolone dramatically improves the prognosis of patients with Wegener's granulomatosis,[3] but 50 percent or more have a relapse within five years, necessitating the resumption of therapy.[3-6] However, prolonged treatment with cyclophosphamide and prednisolone is associated with severe and potentially lethal adverse effects.[5,7,8] Therefore, other methods of preventing relapses are needed.

Active Wegener's granulomatosis is strongly associated with the presence of antineutrophil cytoplasmic antibodies.[4,6,9-11] The titers of these antibodies decline during treatment and become undetectable during remission in about 50 percent of patients,[4,6,9,11] but titers rise again before a relapse.[4,12-14] In several studies respiratory tract or other infections were associated with increases in antineutrophil cytoplasmic antibody titers, clinical illness, or both.[14,15] A possible role for microbial organisms in recurrences of Wegener's granulomatosis is further suggested by reports of beneficial effects of a combination of trimethoprim and sulfamethoxazole (co-trimoxazole) in the treatment of patients with refractory Wegener's granulomatosis or Wegener's granulomatosis confined to the respiratory tract.[16-21]

We designed a double-blind, placebo-controlled, multicenter trial to assess the efficacy of co-trimoxazole in preventing relapses in patients with Wegener's granulomatosis in remission. In addition to the possible influence of co-trimoxazole on the number of relapses, we studied the effect of the agent on the number of infections and on serum antineutrophil cytoplasmic antibody titers.

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*Other participating physicians and centers are listed in the Appendix.

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METHODS

Patients

All physicians in the Netherlands who were treating patients with Wegener's granulomatosis were invited to participate in the study (participating centers are listed in the Appendix). The enrollment of patients started in September 1990 and ended in June 1993. Follow-up was complete through December 1994. Patients eligible for the study were divided into three groups: those with focal segmental necrotizing or crescentic glomerulonephritis on renal biopsy and manifestations of disease in the upper or lower airways compatible with Wegener's granulomatosis, with or without characteristic histologic findings (group 1); those with biopsy-proved Wegener's granulomatosis limited to the airways, with no renal involvement (group 2); and patients fulfilling the 1990 criteria of the American College of Rheumatologists for Wegener's granulomatosis[22] who had positive tests for serum antineutrophil cytoplasmic antibodies during the active phase of their illness but who did not meet the criteria for inclusion in group 1 or 2 (group 3). Patients could be enrolled when their illness was in complete remission with or without treatment with corticosteroids or cyclophosphamide. We excluded patients with a history of adverse reaction to co-trimoxazole or its components, those with impaired renal function (a 24-hour creatinine clearance of less than 30 ml per minute), and those receiving long-term treatment (more than six weeks) with antibiotics or co-trimoxazole. The study protocol was approved by the Medical Ethics Committee of the University Hospital, Groningen, and written informed consent was obtained from each patient.

Study Protocol

After stratification according to group, the patients were randomly assigned to receive co-trimoxazole (800 mg of sulfamethoxazole and 160 mg of trimethoprim; Bactrimel, Roche Pharma, Reinach, Switzerland) or placebo twice daily for 24 months in addition to their usual medication. The treatment assignment was not known to the investigators, the patients, or their physicians. Compliance was assessed by tablet counts. The study medication was stopped if the patient withdrew informed consent, there were side effects of the medication, or the creatinine clearance fell persistently below 30 ml per minute. Other antimicrobial therapy, when deemed necessary by the treating physician, was allowed for no more than six consecutive weeks. In the case of an infection that had to be treated with co-trimoxazole or one of its components or another reason to discontinue the study medication, withdrawal for no more than 28 consecutive days was allowed. Treatment of Wegener's granulomatosis with cyclophosphamide and prednisolone was carried out according to a protocol described previously.[4]

All patients were seen at least once every 3 months during the 24-month treatment period. At each visit the patient was evaluated according to a predefined protocol for signs of disease activity, compliance with the medication regimen, side effects of therapy, and evidence of infections. Required laboratory data included a complete blood count, erythrocyte sedimentation rate, serum C-reactive protein concentration, serum urea and creatinine concentrations, results of microscopical analysis of the urinary sediment, and 24-hour urinary excretion of protein and creatinine. The results were reported on a standard form that was sent to the study coordinator. A blood sample was taken every three months and sent to the Laboratory of the University Hospital, Groningen, for the determination of serum antineutrophil cytoplasmic antibodies by an indirect immunofluorescence technique on ethanol-fixed granulocytes.[4,6,9] According to the protocol, the standardized follow-up ended at 27 months.

Definitions

Patients were considered to have had a relapse if they had one or more of the following new or recurrent findings[14]: active glomerulonephritis, as shown by a decrease of at least 30 percent in renal function in combination with microscopic hematuria with red-cell casts or evidence of acute necrotizing lesions on renal biopsy; pulmonary infiltrates with or without cavitation with rising serum C-reactive protein concentrations in the absence of infection or cancer; sinusitis, otitis, ulceration of nasal mucosa, or a proliferative nasal mass, in combination with necrotizing granulomatous inflammation on biopsy; and progressive mononeuritis multiplex, cranial-nerve palsy, cerebral vasculitis, necrotizing scleritis, orbital pseudotumor, progressive tracheal stenosis with active disease on biopsy, peripheral gangrene, or necrotizing vasculitis of medium-sized or small muscular arteries. Complete remission was defined as the absence of symptoms or signs attributable to active vasculitis in combination with a normal serum C-reactive protein concentration.

A respiratory tract infection was considered to be present if a patient had clinical signs of infection involving the lung, pharynx, trachea, nasal and paranasal tissues, or ear, in combination with a positive culture or serologic evidence or a prompt response to appropriate antibiotic treatment in the absence of microbiologic evidence.[6] Urinary tract infections were defined by the presence of leukocytes in the urine in combination with $\geq 10^5$ colony-forming units of bacteria per milliliter. Other infections were diagnosed on the basis of an evaluation made by the physician responsible for the patient.

Side effects were defined as any symptoms, signs, or biochemical abnormalities possibly related to the study medication, preferably confirmed by rechallenge after the medication was temporarily stopped.

Statistical Analysis

Differences in the frequencies of categorical variables between groups were compared with Fisher's exact test,[23] and continuous variables were compared with Wilcoxon's rank-sum test or matched-pair test.[24] Disease-free intervals, measured from the start of the treatment regimen to the time of the first relapse, were calculated by the Kaplan–Meier method,[25] and differences between groups were evaluated by the log-rank test.[26] Stepwise Cox proportional-hazards regression analysis (BMDP Statistical Software, BMDP, Cork, Ireland) with the disease-free interval as the dependent variable was used to adjust the effect of the study medication for potential independent prognostic factors.[27] The variables were age, sex, disease-free interval before the start of the study, group, type of therapy at the start of the study (prednisolone or cyclophosphamide), status with respect to antineutrophil cytoplasmic antibodies at the start of the study, and creatinine clearance. The occurrence of respiratory tract and non–respiratory tract infections during the study was included as a time-dependent variable. All P values are two-tailed.

RESULTS

Of the 94 patients at the various centers who were eligible for the study, 8 chose not to participate and 2 had a history of possible adverse reactions to co-trimoxazole. Of the remaining 84 patients, 81 entered the study, 2 were excluded because their creatinine clearance was below 30 ml per minute, and 1 withdrew informed consent before starting treatment. There were 41 patients in the co-trimoxazole group and 40 in the placebo group. Of the 22 patients in group 3, 17 had had clinical signs of renal involvement. The base-line characteristics of the patients are shown in Table 1. There were no significant differences in these characteristics between the treatment groups.

Co-trimoxazole was stopped in 8 of the 41 pa-

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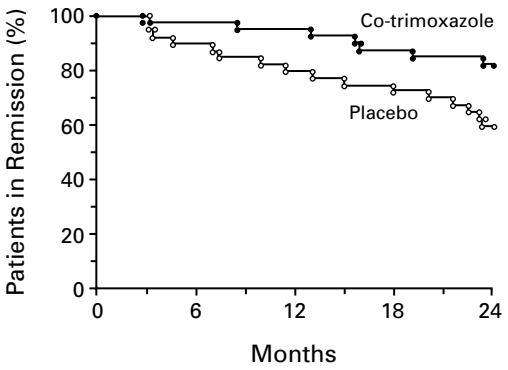
tients (20 percent) because of side effects after a median of 43 days (range, 6 to 125). These consisted of anorexia and nausea (four patients), rash (two patients), presumed interstitial nephritis with fever and eosinophilia (one patient), and asymptomatic hepatotoxic effects (one patient). All side effects resolved after the study medication was stopped. Macrocytic anemia developed in one patient receiving co-trimoxazole, which responded to treatment with folic acid (5 mg daily) and did not necessitate termination of the study medication. Two patients (5 percent) in the placebo group stopped taking the study medication: one had recurrent urinary tract infections and the other withdrew informed consent. All patients who stopped taking the study medication prematurely completed the follow-up and were included in the analysis. One patient in the placebo group died of a myocardial infarction 2.5 months after the start of the study; no signs of active Wegener's granulomatosis were found at autopsy. In the analysis of disease-free interval, data on this patient were censored at the time of death. The median level of compliance with the treatment regimen, as assessed by tablet counts, was 98 percent in the co-trimoxazole group (range, 82 to 100 percent) and 98 percent in the placebo group (range, 83 to 100 percent).

According to life-table analysis, at 24 months of follow-up 82 percent of patients in the co-trimoxazole group were in remission, as compared with 60 percent of patients in the placebo group (relative risk of relapse, 0.40; 95 percent confidence interval, 0.17 to 0.98) (Fig. 1). The results were similar when data on the 10 patients who did not complete the study treatment were censored when the medication was stopped. The reduction in disease activity with co-trimoxazole therapy was especially evident with regard to relapses involving the upper airways (Table 2).

TABLE 1. BASE-LINE CHARACTERISTICS OF 81 PATIENTS WITH WEGENER'S GRANULOMATOSIS, ACCORDING TO TREATMENT.

CHARACTERISTIC	CO-TRIMOXAZOLE (N=41)	PLACEBO (N=40)
Group (no. of patients)		
1	22	22
2	8	7
3	11	11
Sex (M/F)	30/11	28/12
Age (yr)		
Median	56	57
Range	21–82	25–83
Time since diagnosis (mo)		
Median	30	30
Range	1–231	1–178
Length of remission (mo)		
Median	13	14
Range	1–97	1–99
Positive serum test for antineutrophil cytoplasmic antibodies (no. of patients)	28	19
Creatinine clearance (ml/min)		
Median	78	72
Range	32–160	32–125
Cyclophosphamide therapy (no. of patients)	21	20
Prednisolone therapy (no. of patients)	23	19
Completed 24 mo of follow-up (no. of patients)	38	37



NO. OF PATIENTS IN REMISSION			
Co-trimoxazole	41	38	31
Placebo	40	32	23

Figure 1. Disease-free Interval from the Start of Co-trimoxazole or Placebo Treatment to Relapse in Patients with Wegener's Granulomatosis.

The difference in the disease-free interval between the co-trimoxazole group and the placebo group was statistically significant (by the log-rank test) at 24 months (relative risk of relapse, 0.40; 95 percent confidence interval, 0.17 to 0.98).

The annual number of infectious episodes per patient was significantly lower in the co-trimoxazole group during the study than in the placebo group (median, 0.0 vs. 1.0; range, 0.0 to 3.0 vs. 0.0 to 3.75; $P<0.001$). Respiratory tract infections accounted for 86 percent and 76 percent of all infectious episodes in the co-trimoxazole and placebo groups, respectively. There were fewer respiratory tract infections ($P=0.005$) and non–respiratory tract infections ($P=0.05$) in the co-trimoxazole group. A microorganism was identified by culture or serologic testing in only 28 percent of all infections. Six opportunistic infections were identified during the study: five cases of herpes zoster (two in the co-trimoxazole group and three in the placebo group) and one case of cytomegalovirus infection (in the placebo group). In seven of the patients in the placebo group and four of the patients in the co-trimoxazole group who had relapses, the relapses followed a respiratory tract infection within six months.

Proportional-hazards analysis identified only the use of co-trimoxazole ($P=0.02$) and the presence of antineutrophil cytoplasmic antibodies at the start of the study ($P=0.04$) as factors related to the disease-free interval. The relative risks of a relapse of Wege-

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TABLE 2. CLINICAL FEATURES OF WEGENER'S GRANULOMATOSIS AT THE TIME OF RELAPSE IN PATIENTS TREATED WITH CO-TRIMOXAZOLE OR PLACEBO.*

CHARACTERISTIC	CO-TRIMOXAZOLE (N=7)	PLACEBO (N=16)
	no. of patients	
Group		
1	3	10
2	1	3
3	3	3
Clinical feature		
Progressive glomerulonephritis	4	7
Pulmonary lesions	3	2
Nasal or upper-airway lesions†	1	11
Miscellaneous		
Scleritis	1	4
Mononeuritis multiplex	2	0
Dermal granulomatous vasculitis	2	4

*The clinical features are defined in the Methods section. Some patients had more than one clinical feature.

†P=0.03 by Fisher's exact test.

ner's granulomatosis in the proportional-hazards regression model including these two variables were 0.32 (95 percent confidence interval, 0.13 to 0.79) for co-trimoxazole treatment and 2.89 (95 percent confidence interval, 1.12 to 7.45) for a positive serum antineutrophil cytoplasmic antibody test at base line.

During follow-up, titers of antineutrophil cytoplasmic antibodies tended to rise in both groups. At no time, however, was there a statistically significant difference in titer or in the proportion of patients with negative tests for the antibodies in the two groups.

At three months the patients in the co-trimoxazole group had a median increase in the serum creatinine concentration of 17 percent over base-line values (range, −10 to 23 percent; $P<0.001$). This increase persisted throughout the treatment period, but concentrations returned to base-line values three months after the end of the study. In the placebo group the serum creatinine concentration did not change significantly at any time. The patients in the co-trimoxazole group had a small but statistically significant decrease in the hemoglobin concentration at three months (median change, −0.3 g per deciliter; range, −1.2 to 0.7; $P=0.03$), but not thereafter. Also, the mean corpuscular volume of erythrocytes increased slightly from base-line values at 3, 6, 9, and 12 months, but not thereafter.

DISCUSSION

The results of this study demonstrate that prolonged treatment with co-trimoxazole reduces the number of relapses in patients with Wegener's granulomatosis in remission. This reduction was especially evident with respect to relapses involving the upper airways. These results are in accordance with several uncontrolled observations of a beneficial effect of co-trimoxazole in Wegener's granulomatosis,[16-21] but the way in which co-trimoxazole exerts this effect is not clear.

In addition, we found significantly fewer respiratory and non–respiratory tract infections in the patients treated with co-trimoxazole than in those given placebo. This finding suggests that the drug exerts its protective effect by preventing infections. However, only about half the patients who relapsed had respiratory tract infections in the six months preceding the relapse; this finding is in agreement with a previous study.[6] Furthermore, we found no relation between the number of infections and the occurrence of relapses of Wegener's granulomatosis. Analysis of a possible relation between specific infections and relapse of Wegener's granulomatosis was not possible, because the microorganism involved was identified in only 28 percent of all infectious episodes. Given the reported association between nasal carriage of *Staphylococcus aureus* and an increased risk of relapse of Wegener's granulomatosis,[6] it is tempting to postulate that co-trimoxazole treatment reduces the frequency of relapses by eliminating or reducing *S. aureus* in the upper airways.

Some investigators have postulated that co-trimoxazole exerts antiinflammatory effects by interfering with the formation of specific oxygen-derived radicals by activated neutrophils,[28] and activated, superoxide-producing neutrophils are thought to mediate tissue destruction in Wegener's granulomatosis.[29] On the other hand, co-trimoxazole, through its antagonism of folic acid metabolism or other as yet unknown mechanisms, may have immunosuppressive properties.

Drugs used for long-term prophylactic treatment of Wegener's granulomatosis must be safe and well tolerated. Short-term treatment with co-trimoxazole is generally well tolerated, with an incidence of mostly minor adverse effects that is similar to that with most other antimicrobial drugs.[30] Prolonged treatment, as is used for prophylaxis against *Pneumocystis carinii* infection in patients with immunodeficiency, however, is associated with a high incidence of adverse effects.[31] In our study, 20 percent of the patients in the co-trimoxazole group stopped treatment prematurely because of side effects. These side effects were generally mild, with the exception of an episode of presumed interstitial nephritis in one patient. As expected, the serum creatinine concentration increased during co-trimoxazole therapy, but this effect was fully reversible.[32] The hematologic toxicity of co-trimoxazole during prolonged treatment was minor. It therefore seems that, in patients who initially tolerate a high dose of co-trimoxazole, prolonged treatment for 24 months is safe.

Treatment with co-trimoxazole in patients with

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Wegener's granulomatosis could reduce the cumulative dose of immunosuppressive therapy needed in these patients. Whether the beneficial effect of cotrimoxazole on the relapse rate is specific to this drug or is shared by other antimicrobial agents is unknown.

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APPENDIX

The following physicians and hospitals also participated in the study: *Academisch Medisch Centrum, Amsterdam* — J.M. Wilmink, M.G. Koopman, and M.H. Godfried; *Ziekenhuis Maarschalkbos, Baarn* — E. Jansen; *Medisch Centrum, Den Bosch* — P.L.M. van Oijen; *Scheper Ziekenhuis, Emmen* — W. Haanstra; *Medisch Spectrum Twente, Enschede* — J.G.M. Jordans and R.M.L. Brouwer; *Martini Ziekenhuis, Groningen* — J.D.M. Gökemeijer and W. Geerlings; *University Hospital, Leiden* — F.J. van der Woude, C. Hagen, and C.J. Doorenbos; *University Hospital, Maastricht* — C.A. Gaillaard; *St. Antonius Ziekenhuis, Nieuwegein* — E.J. ter Borg; *University Hospital, Nijmegen* — J.H.M. Berden, L.J.M. Reichert, and R.G.W.L. Tiggeler; *University Hospital, Utrecht* — R.J. Hené; and *Sophia Ziekenhuis, Zwolle* — T. Tjabbes.

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