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Boomsma, Maarten Michiel

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Trimethoprim-sulfamethoxazole monotherapy for active loco-regional or limited Wegener's granulomatosis

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Submitted for publication
Abstract

Incidental reports suggest that Wegener's granulomatosis (WG) limited to the upper and lower airways can be treated with trimethoprim-sulfamethoxazole. We performed a cohort study to evaluate oral trimethoprim-sulfamethoxazole as initial therapy to control disease activity in untreated patients with active loco-regional or limited WG. Consecutive untreated patients, either at diagnosis or during relapse, with biopsy proven active WG limited to the upper and lower airways presenting since 1993 were eligible. Treatment consisted of oral trimethoprim-sulfamethoxazole 160/800 mg bid. Treatment failure was defined as relapse of disease activity or need for additional treatment to control disease activity. Thirty-one patients, 25 at diagnosis and 6 during relapse of active WG were included. Twenty-seven patients responded (87%, 95% confidence interval, 70 to 96%). Nine achieved partial and eighteen complete remission of WG disease activity, respectively, after 3 (median, range 1 to 15) months of therapy. Two patients developed side effects, while 2 patients did not respond. During follow up 5 of 9 after partial and 6 of 18 patients after complete remission relapsed after 14 (median, range 2 to 32) months. Treatment failure was more likely in patients with disease activity outside the ENT region and in patients with a Staphylococcus aureus negative nasal culture at initiation of therapy. Actuarial disease controlled survival on intent to treat basis with trimethoprim-sulfamethoxazole was 70%, 60%, and 36% at 12, 24, and 36 months of therapy, respectively. In conclusion, trimethoprim-sulfamethoxazole treatment leads to partial or complete remission in a substantial proportion of patients presenting with active WG limited to the upper and lower airways.

Introduction

Wegener's granulomatosis is a disease of presumed auto-immune origin, characterized by necrotizing granulomatous inflammation of the upper and lower airways, in combination with systemic necrotizing small vessel vasculitis and glomerulonephritis (Jennette et al., 1994). Prolonged immunosuppressive therapy with cyclophosphamide and corticosteroids leads to remission of disease activity in most patients, however, at the costs of significant short and long term treatment related toxicity (Hoffman et al., 1992). In many patients Wegener's granulomatosis begins with a period of months or years of disease activity confined to the upper airways without systemic involvement, i.e. loco-regional Wegener's granulomatosis (Gross, 1989). As infections, especially of the upper airways, are thought to trigger disease activity (Pinching et al., 1980), and cases of Wegener's granulomatosis limited to the upper and lower airways who have been successfully treated with trimethoprim-sulfamethoxazole alone or as additional treatment have been published, the use of this relatively non-toxic antibiotic treatment has been advocated in patients with loco-regional or limited Wegener granulomatosis (DeRemee, 1988). Controlled data on the efficacy of this treatment, however, are not available. To evaluate the potential efficacy and limitations of this treatment, we
performed a cohort study of consecutive patients with Wegener's granulomatosis presenting with disease activity limited to the upper and lower airways treated with trimethoprim-sulfamethoxazole only, i.e. without concomitant immunosuppressive therapy.

**Patient and Methods**

Consecutive patients with an episode of biopsy-proven (Devaney et al., 1990), active Wegener's granulomatosis limited to the upper and lower airways, at diagnosis or during relapse, presenting since 1993 were eligible for treatment with trimethoprim-sulfamethoxazole monotherapy, if they fulfilled the following criteria: absence of symptoms such as fever (>38.0°C), significant involuntary weight loss (>2 kg/month), erythrocyturia, or progressive renal function loss; no signs or symptoms of alveolar hemorrhage or respiratory failure, peripheral or central neurological, or gastro-intestinal involvement. Patients with concomitant malaise, arthralgias and mild (non-necrotizing) episcleritis were included. Patients at diagnosis were excluded if they had received corticosteroids or other immune suppressive drugs. Patients during relapse were allowed to be on low dose corticosteroids and/or other immune suppressive drugs. Patients were however excluded if they had received prolonged (>4 weeks) therapy with antibiotics in the 6 months prior to the episode of active Wegener's granulomatosis or had a history of adverse events on trimethoprim or sulphonamide type drugs. After informed consent was obtained, the patient was started on oral trimethoprim-sulfamethoxazole 160/800 mg twice daily. Local therapy with 0.1% dexamethason eye drops was allowed for patients with episcleritis during the first 2 to 4 weeks. Patients were seen at our outpatient clinic every 2 weeks for the first 8 weeks and monthly thereafter. A careful history and physical examination were taken at every visit, blood was drawn for determination of C-reactive protein level, creatinine, hemoglobin, white blood cell count, platelets and antineutrophil cytoplasmic antibody (ANCA) titer. Disease activity of Wegener's granulomatosis was scored every month using the Birmingham Vasculitis Activity Score (BVAS) (Luqmani et al., 1994). Serum ANCA titer was determined by indirect immunofluorescence on ethanol fixed human neutrophils as described previously (van der Woude et al., 1985). Antigenic specificity for proteinase-3, myeloperoxidase or human neutrophil elastase of ANCA was tested by antigen specific capture ELISA (Cohen Tervaert et al., 1990). ANCA negative samples were subsequently tested by antigen specific direct ELISA (Boomsma et al., 2000).

Treatment failure was defined as the need for alternative or additional treatment to control Wegener's granulomatosis, or relapse of disease activity after initial response to trimethoprim-sulfamethoxazole. Complete remission was defined as the total absence of symptoms or signs attributable to active Wegener's granulomatosis (BVAS = 0) in combination with a normal serum C-reactive protein level (<3 mg/l). Partial remission was defined as an improvement in disease activity score and C-reactive protein level without fulfilling the criteria for complete remission. Nasal endoscopy, with biopsy if disease activity was suspected, was performed 3
to 6 months after start of trimethoprim-sulfamethoxazole in all patients to assess local disease activity. The study was carried out in accordance with the Declaration of Helsinki of 1967, as last revised in Edinburgh in October, 2000. See www.wma.net.

Data are presented as median with total range. Differences between groups in categorical quantities were tested with Fischer’s exact test. Disease free survival during trimethoprim-sulfamethoxazole treatment was estimated with the Kaplan-Meier method and survival curves were generated using GraphPad Prism™ software. Differences in disease free interval were studied by log-rank test. Hazard ratios are reported as relative risks with 95% confidence intervals. A two-sided p-value of < 0.05 was considered to indicate statistical significance.

Table 1 Clinical involvement and disease activity as indicated by Birmingham Vasculitis Activity Score (BVAS) and serum C-reactive protein level in 31 patients with active loco-regional or limited Wegener’s granulomatosis treated with trimethoprim-sulfamethoxazole.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose</td>
<td>31</td>
<td>(100%)a</td>
</tr>
<tr>
<td>Ears</td>
<td>9</td>
<td>(29%)</td>
</tr>
<tr>
<td>Eyes</td>
<td>7</td>
<td>(23%)</td>
</tr>
<tr>
<td>Trachea</td>
<td>2</td>
<td>(6%)</td>
</tr>
<tr>
<td>Lungs</td>
<td>3</td>
<td>(10%)</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>11</td>
<td>(35%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>21</td>
<td>(68%)</td>
</tr>
<tr>
<td>BVAS score b</td>
<td>7</td>
<td>(5-11)</td>
</tr>
<tr>
<td>C-reactive protein level (mg/l) b,c</td>
<td>14</td>
<td>(&lt;3-96)</td>
</tr>
</tbody>
</table>

a Progressive destruction of bone structures in 15 patients
b Median (total range)
c Normal value < 3 mg/l

Results

Thirty-one consecutive patients, 10 males and 21 females, aged 47 years (29 to 86), were included. Fourteen patients had disease activity confined to the ENT region (i.e. loco-regional Wegener’s granulomatosis), and 17 patients had disease activity in the ENT region in combination with arthralgias, episcleritis or pulmonary lesions (i.e. limited Wegener’s granulomatosis). Twenty-five patients were included at diagnosis during their first episode of active Wegener’s granulomatosis, six patients during relapse after a previous period of complete remission. In these six patients with relapse the period since the previous disease activity episode was 22 months (13 to 40) and immunosuppressive therapy was stopped 7 and 28 months prior to the current episode in two patients. Four patients were still using a low dose azathioprine at the moment of the current episode. The dosage of azathioprine was further tapered after trimethoprim-sulfamethoxazole treatment was started. Twenty-six
patients (84%) had detectable ANCA as measured by antigen specific capture ELISA at the time of inclusion, 20 with specificity for proteinase 3 and 6 with specificity for myeloperoxidase, respectively. All but one of these 26 patients also tested positive for ANCA by indirect immunofluorescence. Five patients were ANCA negative by indirect immunofluorescence, antigen specific capture ELISA, and antigen specific direct ELISA. Twenty-five of 31 patients (81%) had nasal swab cultures positive for Staphylococcus Aureus at inclusion. Clinical characteristics at the moment of inclusion are given in Table 1. All patients had nasal mucosal abnormalities with necrotizing granulomatous inflammation with or without vasculitis on nasal biopsy.

![Graph](image)

**Figure 1** Disease controlled survival with trimethoprim-sulfamethoxazole monotherapy in 31 patients with active Wegener's granulomatosis limited to the upper and lower airways. The small vertical lines above the curve indicate censored subjects. The number of patients still on trimethoprim-sulfamethoxazole treatment at risk of relapse of Wegener's granulomatosis is indicated below the horizontal axis.

Treatment with trimethoprim-sulfamethoxazole was initially successful in 27 of 31 patients (87%, 95% confidence interval, 70 to 96%), with complete remission in 18, and partial remission in 9 patients, respectively. Of 14 patients with disease activity confined to the ENT region all responded (11 complete, 3 partial) as compared to 13 (7 complete, 6 partial) of 17 patients with ENT involvement in combination with arthralgias, episcleritis or pulmonary lesions (P = 0.067). In responding patients time to maximal treatment response was 3 months (1 to 15). Treatment with trimethoprim-sulfamethoxazole had to be stopped in 2 patients due to fever and rash occurring 7 and 41 days after starting therapy, respectively, while 2 patients showed no improvement and local disease progression after 1-2 months of therapy. All were treated with cyclophosphamide and prednisolone followed by prompt complete remission.
Chapter 8

Estimated disease controlled survival with trimethoprim-sulfamethoxazole monotherapy was 70% (95% confidence interval, 53 to 87%), 60% (95% confidence interval, 41 to 79%), and 36% (95% confidence interval, 14 to 58%) at 12, 24, and 36 months, respectively (Figure 1). Median disease-free survival on trimethoprim-sulfamethoxazole therapy was 25 months. Twelve patients, all with persistent complete remission, are still on trimethoprim-sulfamethoxazole monotherapy with a follow up of 27 months (10 to 95). In the 18 patients with complete remission on trimethoprim-sulfamethoxazole disease-free survival at 24 months was 87% (95% confidence interval, 69 to 100%).

Table 2 Clinical involvement and disease activity as indicated by Birmingham Vasculitis Activity Score (BVAS) and serum C-reactive protein level of 11 relapsing patients with Wegener's granulomatosis after initial response to treatment with trimethoprim-sulfamethoxazole.

<table>
<thead>
<tr>
<th>Condition</th>
<th>BVAS Score</th>
<th>C-reactive protein level (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose (biopsy-proven)</td>
<td>5</td>
<td>(45%)</td>
</tr>
<tr>
<td>Ears</td>
<td>1</td>
<td>(9%)</td>
</tr>
<tr>
<td>Eyes</td>
<td>4</td>
<td>(36%)</td>
</tr>
<tr>
<td>Trachea</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Lungs</td>
<td>3</td>
<td>(27%)</td>
</tr>
<tr>
<td>Renal</td>
<td>3</td>
<td>(27%)</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>(9%)</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>7</td>
<td>(64%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>6</td>
<td>(55%)</td>
</tr>
<tr>
<td>BVAS score</td>
<td>9</td>
<td>(7-29)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>13</td>
<td>(4-136)</td>
</tr>
</tbody>
</table>

*a* Median (total range)  
*b* Normal value < 3 mg/l

Figure 2 Disease controlled survival in 27 responding patients with active Wegener's granulomatosis limited to the upper and lower airways according to partial or complete remission with trimethoprim-sulfamethoxazole monotherapy. The small vertical lines above the curve indicate censored subjects. (partial remission versus complete remission, P < 0.001). Broad line = partial remission (n = 9); thin line = complete remission (n = 18).
During follow up 11 patients, 5 of 9 (56%) after partial and 6 of 18 (33%) after complete remission, relapsed 14 months (2 to 32) after start of trimethoprim-sulfamethoxazole treatment (relative risk 5.8; 95% confidence interval 4.6 to 21.3, P < 0.001) (Figure 2). Clinical characteristics at the moment of relapse are given in Table 2. In patients who tolerated trimethoprim-sulfamethoxazole treatment (n = 29), significantly more *Staphylococcus aureus* negative patients failed therapy as compared to *Staphylococcus aureus* positive patients (relative risk 44.9; 95% confidence interval 4.8 to 421.3, P < 0.0001)(Figure 3). As all *Staphylococcus aureus* positive patients became negative for these microorganisms after trimethoprim-sulfamethoxazole treatment, we were unable to demonstrate a relation between these microorganisms during followup and response or relapse. Patients with ENT involvement in combination with arthralgias, episcleritis or pulmonary lesions (n = 15) who tolerated trimethoprim-sulfamethoxazole treatment were more prone to treatment failure as compared to patients with initial disease activity confined to the ENT region (n = 14) (relative risk 3.0; 95% confidence interval 1.0 to 9.2, P = 0.05). ANCA titers by indirect immunofluorescence, which were positive in 21 of 27 responding patients decreased by at least 2 titer steps (fourfold) within the first 12 months in 13 patients. These 13 patients were, however, not more prone to relapses as compared to patients with constant or increasing ANCA titers (n = 8) (relative risk 1.3; 95% confidence interval 0.4 to 5.0, P = 0.63).

**Discussion**

Since the initial anecdotal reports on the successful treatment of Wegener's granulomatosis with trimethoprim-sulfamethoxazole, its place as monotherapy or additional therapy in the therapeutic armamentum for this disease has been unclear (DeRemee, 1988; Leavitt et al., 1988, Stegeman et al., 1997). Our study, although of limited size, shows an initial response rate to trimethoprim-sulfamethoxazole monotherapy of 87% with complete remission in 58% of 31 consecutive well-defined patients with untreated active loco-regional or limited Wegener's granulomatosis. The disease was controlled in 60% for at least 24 months analyzed.
on an intent to treat basis. In patients obtaining a complete remission on trimethoprim-sulfamethoxazole the disease controlled survival was a high as 87% at 24 months. DeRemee has reported remission in 14 of 15 patients with limited Wegener's granulomatosis treated with trimethoprim-sulfamethoxazole only (DeRemee, 1988), but detailed follow up data are only presented for few of them (DeRemee et al., 1985). Reinhold-Keller reported partial or complete remission in 11 of 19 patients (58%) with limited Wegener's granulomatosis treated with trimethoprim-sulfamethoxazole (Reinhold-Keller et al., 1996). However, trimethoprim-sulfamethoxazole was the initial and only treatment in only 10 patients. Le Thi Huong Du reported a beneficial response in 2 of 7 patients with varying disease extent of Wegener's granulomatosis treated initially with trimethoprim-sulfamethoxazole (Le Thi Huong Du et al., 1990). Finally, Hoffman reported clinical improvement in 3 of 9 patients with limited Wegener's granulomatosis treated with trimethoprim-sulfamethoxazole, but none of the patients achieved remission (Hoffman, 1996).

Given the observed response rate, trimethoprim-sulfamethoxazole may be advocated as the initial treatment in patients with loco-regional Wegener's granulomatosis with only ENT involvement. Even in patients with Wegener's granulomatosis with disease activity in the ENT region in combination with mild episcleritis, pulmonary lesions, and arthralgias, i.e. limited Wegener's granulomatosis, trimethoprim-sulfamethoxazole may obviate the need for the more toxic conventional treatment with cyclophosphamide and corticosteroids for prolonged periods. Our data do, however, suggest that the chance for obtaining a complete remission with trimethoprim-sulfamethoxazole monotherapy in the latter group is lower than with Wegener's granulomatosis strictly confined to the ENT region. Also, the relapse risk tended to be increased in patients who had initially active Wegener's granulomatosis outside the ENT region. Importantly, during trimethoprim-sulfamethoxazole treatment some patients relapse or progress with severe renal and pulmonary disease activity in combination with only mild or absent upper airways symptoms. The same phenomenon was noted in a randomized, placebo controlled study with trimethoprim-sulfamethoxazole treatment for the prevention of relapses of Wegener's granulomatosis (Stegeman et al., 1996). Therefore, treatment with trimethoprim-sulfamethoxazole in a patient with loco-regional or limited WG should include strict follow up to detect early systemic relapse or progression, which can occur despite improvement of upper airways symptoms.

It is currently not clear how trimethoprim-sulfamethoxazole exerts its beneficial effect. We found treatment with trimethoprim-sulfamethoxazole to be beneficial in Staphylococcus aureus positive patients with Wegener's granulomatosis, while it was not in the small number of Staphylococcus aureus negative patients in our study. In addition, we have previously reported an association between nasal carriage of Staphylococcus aureus and an increased risk for relapse of Wegener's granulomatosis (Stegeman et al., 1994). It is, therefore, tempting to postulate that trimethoprim-sulfamethoxazole suppresses the presence of Staphylococcus aureus in the upper airways and thereby reduces disease activity. We were, however, unable
to demonstrate a relation between recurrence or persistence of *Staphylococcus aureus* and treatment failure of trimethoprim-sulfamethoxazole during followup. Others have postulated that sulphonamide drugs exert anti-inflammatory effects through interference with the formation of specific oxygen derived radicals by activated neutrophils (Roberts et al., 1990). Alternatively, trimethoprim-sulfamethoxazole by its antagonism of folic acid metabolism or other as yet unknown mechanisms may have immunosuppressive properties. As *Staphylococcus aureus* negative patients seem not to benefit from trimethoprim-sulfamethoxazole treatment, it is unlikely that trimethoprim-sulfamethoxazole exert its effect solemnly by aspecific anti-inflammatory effects.

In conclusion, a substantial portion of patients with active Wegener's granulomatosis limited to the upper and lower airways can be initially controlled with oral trimethoprim-sulfamethoxazole treatment only. Especially in patients with initially a complete response on trimethoprim-sulfamethoxazole long term control of the disease seems possible. Whether trimethoprim-sulfamethoxazole treatment in these patients leads to long term adequate disease control and to a reduction in the cumulative cyclophosphamide and corticosteroid dose as compared to conventional treatment, can only be established by carefully conducted prospective, randomized multi-center studies.

**Acknowledgements**

We thank Dr Cees Buiter (Department of ENT surgery, University Hospital Groningen) for his assistance in diagnosing and evaluating the patients.

**Literature**


Chapter 8