Abstract

Wegener’s granulomatosis (WG) has two different clinical phases: the initial phase and generalized phase. In patients with generalized WG, both steroids and cyclophosphamide have generally been used. We report a case of generalized WG that was temporarily, but successfully treated with sulfamethoxazole-trimethoprim (S/T) alone. S/T therapy reduced the elevated levels of soluble IL-2 receptor and IL-6 in parallel with improvement of the patient’s symptoms and urinary protein excretion. In view of the high incidence of lethal adverse effects of cytotoxic drugs, S/T monotherapy may be worth trying not only for initial phase WG but also for generalized WG with careful follow-up when the patient is not acutely ill.

Key words: soluble IL-2 receptor, IL-6, proteinuria

Introduction

The effectiveness of sulfamethoxazole-trimethoprim (S/T) for Wegener’s granulomatosis (WG) was first reported in 1985 by DeRemee et al (1). Since then, several therapeutic trials of S/T in WG have been performed (2–15). Recent prospective trials have indicated the effectiveness of S/T as first-line therapy for patients with “initial phase” WG, i.e., symptoms restricted to the upper and/or lower airways without constitutional symptoms or systemic vasculitis. On the other hand, patients with “generalized” WG, who have renal involvement and systemic vasculitis, are recommended to receive the standard Fauci’s regimen consisting of a steroid and a cytotoxic agent. However, this regimen has the risk of causing severe concomitant opportunistic infections that often lead to death. Although this severe disease requires strong treatment, it is also true that a less toxic regimen is urgently needed.

We report a patient with generalized WG who achieved complete remission of all symptoms, including nephropathy, with S/T monotherapy instead of the standard toxic regimen, and discuss the possibility of using S/T monotherapy to treat generalized WG.

Case Report

A 73-year-old woman was admitted to another hospital on November 1, 1996, for examination of a coin lesion found in the right lower lung lobe during a regular health check. She had noticed fatigue, loss of appetite, low-grade fever, and nasal obstruction for 1 week prior to admission. On admission, congestion of both eyes and high fever (38.5°C) were found together with microscopic hematuria and proteinuria. Her high fever continued for two weeks despite the administration of antibiotics, and was followed by hearing loss and the development of painful papulopurpuric lesions on the extremities. On November 18, a chest X-ray film showed a new infiltrative lesion in the right upper lobe. On the following day, she had massive rectal bleeding (about 1,000 ml). On November 26, she was transferred to our hospital for further evaluation.

On admission, physical examination revealed a temperature of 37.1°C, a blood pressure of 122/74 mmHg, a pulse rate of 76 beats/min, and a respiration rate of 18 beats/min. She was drowsy and could not stand up. Congestion of both eyes and papulopurpuric lesions of the extremities were noted (Fig. 1). Laboratory tests showed a CRP of 1.1 mg/dl, an erythrocyte sedimentation rate of 52 mm/h, blood urea nitrogen of 16.4 mg/dl, and serum creatinine of 0.43 mg/dl. There was also 3+ microhematuria (25-30 RB C/high-power field) and proteinuria of 0.6 g/day. Rheumatoid factor and antinuclear antibody were both negative. Other immunological tests, including anti-DNA antibody, anti-ss-A/Ro antibody, anti-ss-B/La antibody, and anti-dsDNA-IgG antibody, were negative. Proteinase-3 antineutrophil cytoplasmic antibody (PR-3 ANCA) and...
myeloperoxidase antineutrophil cytoplasmic antibody (MPO ANCA) were positive at a low titer (14 and 22 EU, respectively) by enzyme-linked immunosorbent assay (ELISA). By the indirect immunofluorescent method, antineutrophil cytoplasmic antibody (ANCA) was positive with a cytoplasmic pattern. Her chest X-ray film showed an infiltrative lesion in the right upper lobe area as well as a coin lesion in the right lower lobe (Fig. 2). On proctoscopy, a rectal ulcer was recognized. She also had corneal thinning and ulceration associated with scleritis.

Biopsy specimens were taken from the skin, rectum, nasal mucosa, kidney, and lung. The skin biopsy disclosed granulomatous vasculitis in the upper dermis (Fig. 3), but the rectum and nasal mucosa did not reveal any specific findings. Percutaneous renal biopsy was performed on December 9. The specimen contained 16 glomeruli, none of which were obsolescent or crescentic. All of the glomeruli showed mild mesangial proliferation without any deposition of immunoglobulin or complement on immunofluorescence analysis (Fig. 4). Electron microscopy demonstrated no electron-dense deposits in the glomeruli and there were no alterations of the tubulointerstitium. Necrotizing arteritis was not found in the kidney specimen. Transbronchial lung biopsy revealed infiltration of leukocytes.
during careful follow-up, prednisolone and cyclophosphamide would also be added to her therapy. The patient was treated with sulfamethoxazole (1,600 mg/day) and trimethoprim (320 mg/day) from January 18, 1997. Her symptoms improved after two weeks, including low grade fever, loss of appetite, nasal obstruction, congestion of both eyes, and hearing loss. In addition, her proteinuria, lung infiltrates, and papulopurpuric lesions of the extremities completely disappeared after one month of S/T monotherapy. Microscopic hematuria also disappeared completely within 3 months of starting treatment, while PR-3 ANCA and CRP were normalized after one month.

In November 1997, eight months after she achieved remission, the PR-3 ANCA titer increased to 291 EU along with elevation of the CRP (8.2 mg/dl) and ESR (121 mm/h). Although there was no evidence of infection, including upper respiratory tract symptoms, and no clinical findings such as proteinuria related to WG were observed, standard therapy with prednisolone (30 mg/day, 0.66 mg/kg body weight) and cyclophosphamide (50 mg/day, 1.1 mg/kg body weight) was added to prevent the relapse of WG. Soon after starting this treatment, PR-3 ANCA, CRP, and ESR were all normalized.

During the clinical course, we measured the serum levels of various cytokines, including IL-2, IL-6, TNF-α, and soluble IL-2 receptor (sIL2r). As shown in Table 1, S/T monotherapy reduced the levels of sIL2r and IL-6 in parallel with the decrease of urinary protein excretion. When PR-3 ANCA increased, both sIL2r and IL-6 also increased again.

**Discussion**

In 1996, Reinhold-Keller et al reviewed 11 earlier reports about the effectiveness of S/T for patients with generalized WG (13) and showed that 29 out of 30 patients treated with S/T achieved clinical improvement. However, since 13 of these patients received concomitant immunosuppressive therapy, it remained unclear whether S/T alone was effective. Therefore, a prospective study was done to clarify the effectiveness of S/T, and it showed that S/T monotherapy induced remission in 58% of patients with their initial episode of WG. Among patients with generalized WG in remission, however, S/T therapy failed to show any favorable effect with respect to maintaining the remission. In contrast, Stegeman et al reported in the same year that treatment with S/T reduced the incidence of relapse in patients who had generalized WG in remission (14). It remains unclear why these conflicting results were obtained.

Both of the above-mentioned authors used S/T to prevent the relapse of generalized WG in remission, and there have been only a few previous reports on the value of S/T for achieving remission of generalized WG (4). Indeed, both of these authors used prednisolone and cyclophosphamide as their standard remission induction therapy, as proposed by Hoffman et al (10). The standard therapy for generalized WG achieves a 75% remission rate and dramatically improves the course of the disease. However, treatment-related morbidity is often quite severe. The level of disease activity and the extent of the organs affected by generalized WG vary from patient to patient. Some patients have fulminant life-threatening WG, while others have generalized disease that is not life-threatening. Not all clinical manifestations of WG require standard therapy. If a major exacerbation occurs as defined by Kallenberg et al (17), including a rapid decrease of creatinine clearance, pulmonary infiltrates combined with dyspnea, cerebral vasculitis, peripheral neuropathy, cranial nerve palsy, orbital pseudotumor, necrotizing scleritis, tracheal stenosis, myocardial infarction, and massive gastrointestinal bleeding secondary to vasculitis, standard therapy should be selected carefully.

The reasons why we chose S/T monotherapy in this case were as follows: 1) Disease activity was relatively mild and the patient was not acutely ill. Massive rectal bleeding occurred once, but was not confirmed to be due to vasculitis by biopsy and no recurrence of gastrointestinal bleeding was seen. None of the other criteria for a major exacerbation proposed by Kallenberg et al (17) were seen in our case. Although the affected organs were widespread, the activity was not severe. 2) Severe glomerulitis or disseminated vasculitis was not proven by pathological examination. Granulomatous vasculitis was only detected in the skin biopsy specimen. On the whole, the pathological findings suggested mild disease in our case. 3)
Although ANCA was positive, the titre was low. The ANCA titre is reported to reflect disease activity (18, 19), therefore the low ANCA suggested that disease activity was not high in our patient. 4) Although we administered several antibiotics, elevation of CRP and fever did not respond. Serial bacterial culture studies only revealed *Staphylococcus aureus* in the nasal discharge. However, the possibility of occult infection was not fully ruled out, so the use of prednisolone and cyclophosphamide could have had significant risks for this relatively well and stable patient, including opportunistic infection and death. For these reasons, we first chose S/T monotherapy. When S/T is used alone, patients must be monitored frequently for evidence of disease progression. However, if used with appropriate caution in patients without life-threatening disease, S/T monotherapy can be effective and thus may avoid the potentially severe complications of cytotoxic therapy.

We think that the indications for S/T monotherapy are the initial phase of WG and some patients with less severe generalized WG. When S/T is used to treat generalized WG, the following criteria should be fulfilled: 1) The disease is not rapidly progressive and is not life-threatening. 2) Severe glomerulitis and/or disseminated vasculitis do not exist. 3) The ANCA titre is relatively low. Under these conditions, S/T monotherapy may be selected when there is a risk of bacterial infection, a risk of exacerbating and/or causing fulminant progress of existing viral hepatitis (B or C), or when the patient is so old that severe side effects of cytotoxic therapy such as myelosuppression are thought to be highly likely. When the patient is proved to have nasal carriage of *Staphylococcus aureus*, S/T may be added as an adjuvant to the standard therapy during initial management.

The reason why S/T is effective for WG has not been fully elucidated, although two possible explanations have been suggested (12, 14, 15, 20). One is that S/T may eliminate some unknown infectious agent that triggers the onset of WG. Despite intensive research, no causative microorganism has been detected to date. However, Stegeman et al reported (14) that the relapse of WG was related to chronic nasal carriage of *Staphylococcus aureus* and upper airway infection, thus infection seems to at least influence the course of the disease. S/T may be effective against the putative unknown infectious agent.

The other proposed explanation is that S/T may have some immunosuppressive action (12, 14). The pathogenesis of WG includes changes and activation of the immune system, resulting in an increase in the production of inflammatory cytokines like TNF-α, IL-2, and IL-6 (20). TNF-α then stimulates and primes neutrophils to express PR-3 or other lysozomal enzymes on the cell surface (21, 22). TNF-α can also stimulate vascular endothelial cells to express endothelial PR-3 and adhesion molecules, and thus facilitates contact between neutrophils and vascular endothelial cells. Activated neutrophils can produce reactive oxygen species and also release lysozomal enzymes after reacting with circulating ANCA (23, 24), all of which can participate in tissue damage. What is the possible site of action of S/T? In 1980, Anderson et al reported that a high concentration of S/T inhibits phagocytic H₂O₂ production by neutrophils *in vitro* (25), and thus S/T may have a direct influence on neutrophil function. However, the same authors also reported that administration of four ST tablets daily to healthy volunteers did not alter neutrophil function *in vivo*. To determine whether S/T has immunosuppressive properties, the following possibilities should be further investigated: 1) suppression of local cytokine production, 2) inhibition of neutrophil priming, and 3) suppression of ANCA production by inhibiting T cell activation. Regarding the relationship between cytokines and glomerulonephritis, McCarthy et al (26) have reported that TNF-α increases the albumin permeability of isolated rat glomeruli through the generation of superoxide. It is also known that IL-6 mRNA expression is increased in peripheral blood T cells from patients with IgA nephropathy and is positively correlated with urinary protein excretion (27).

Accordingly, it seemed important to determine the serum levels of these cytokines in the present patient. As shown in Table 1, S/T monotherapy reduced the serum levels of soluble IL-2 receptor and IL-6 along with a decrease of proteinuria and PR-3 ANCA. These results suggest that S/T may inhibit T

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<tr>
<th>Cytokines</th>
<th>Pretreatment ('96/Nov 28)</th>
<th>In remission ('97/Apr 10)</th>
<th>ANCA flare-up ('97/Dec 3)</th>
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<tbody>
<tr>
<td>IL-2 (U/ml)</td>
<td>0.8&gt;</td>
<td>0.8&gt;</td>
<td>0.8&gt;</td>
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<tr>
<td>sIL2r (U/ml)</td>
<td>1.070</td>
<td>386</td>
<td>828</td>
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<tr>
<td>TNF-α (pg/ml)</td>
<td>5&gt;</td>
<td>5&gt;</td>
<td>5&gt;</td>
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<tr>
<td>IL-6 (pg/ml)</td>
<td>55.4</td>
<td>6.8</td>
<td>25.4</td>
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<tr>
<td>PR-3 ANCA (EU)</td>
<td>14</td>
<td>10&gt;</td>
<td>286</td>
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<tr>
<td>Urinary protein (g/day)</td>
<td>0.6</td>
<td>0</td>
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Normal range: IL-2, 0.8>; sIL2r, 184–552; TNF-α, 5>; IL-6, 4.0>; PR-3 ANCA, 10>; and proteinuria, negative. The levels of IL-6, sIL2r, and PR-3 ANCA were decreased markedly by S/T monotherapy and the remission lasted for approximately 9 months.
cell activation and may suppress cytokine production. It is interesting to note that sIL2r increased again along with the increase of PR-3 ANCA.

Although the remission achieved with S/T monotherapy was not so long in the present patient, we still think it is significant that she achieved remission without steroids or cyclophosphamide. WG is a chronic and relapsing disease, so steroids and cyclophosphamide are usually administered for long periods. If these drugs are stopped, more than 50% of patients suffer a relapse that requires re-administration of standard remission induction therapy. As a result, the total doses of these drugs become very high. The risk of bladder cancer or hematologic malignancy increases when cytotoxic drugs are used over the long term. In the view of the chronic course of WG and the risk of side effects from long-term use of cytotoxic drugs as well as short-term dangers like opportunistic infection, it may be useful to employ S/T for disease control, even temporarily, without steroids or cytotoxic drugs.

In conclusion, S/T monotherapy induced the remission of generalized WG and proteinuria was completely resolved. Although the remission did not last long, S/T seems to be effective even for patients with generalized WG. The mechanism by which S/T improved vasculitis-related organ damage may be related to its anti-cytokine effect.

References
