CASE REPORT

Two Cases of Severe Bronchiectasis Successfully Treated with a Prolonged Course of Trimethoprim/Sulfamethoxazole

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Two patients with severe bronchiectasis, one patient without other disease and the other with hyper IgE syndrome, were successfully treated with long-term therapy with low doses of trimethoprim and sulfamethoxazole (TMP-SMZ). Recurrent respiratory infections with productive cough and high fever were resistant to various antibiotics and often disturbed the patients’ activities in daily life. However, they showed marked improvement following TMP-SMZ therapy, which was started for methicillin-resistant Staphylococcus aureus (MRSA) infection. MRSA disappeared some months later, but Pseudomonas aeruginosa appeared again in the sputum. Both patients, however, have remained free from symptoms for over one year.

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Key words: hyper IgE syndrome, lower respiratory infection, methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa

Introduction

It has been reported that trimethoprim-sulfamethoxazole (TMP-SMZ) is effective for short-term and long-term use in the treatment of chronic respiratory infections (1, 2). Recently, however, TMP-SMZ has not been considered the drug of first choice for various bacterial infections due to its side effects and because of the development of new antibiotics. We describe here two cases with severe bronchiectasis successfully treated with a long-term course of TMP-SMZ.

Case Report

Case 1 (Fig. 1)

A 53-year-old male had an operation for chronic sinusitis when he was 17 years old. He remained well without history of pulmonary tuberculosis until 48 years of age, when he noted susceptibility to colds. He visited our hospital on November 12, 1988, with chief complaints of high fever and productive cough. A chest roentgenogram showed reticulonodular shadow and bronchial wall thickening in both lung fields and infiltration in the right upper field. He was admitted with a diagnosis of bronchiectasis with acute pneumonia. In the following three years, he was again admitted several times for the same symptoms which disturbed his activity in daily life. Hemophilis influenzae and/or Pseudomonas aeruginosa (P. aeruginosa) were isolated from his sputum. He had received many different antibiotics including ampicillin, piperacillin sodium, sulbactam tosylate, cefazolin sodium, cefotiam pivoxil, clindamycin, ciprofloxacin hydrochloride and ofloxacin. They were sensitive to at least one antibiotic. However, other antibiotics were tried due to repeated fever. Analysis of his blood showed slight leukocytosis (5,000–10,800). Erythrocyte sedimentation rate (ESR) had increased to 30–60 mm/h and CRP was 2+ to 4+. Arterial blood gas analysis on November 11, 1989, showed hypoxemia (PaO2, 56.8 Torr, PaCO2, 40.7 Torr; pH 7.410). Various oral antibiotics taken in rotation were effective only temporarily, and high fever often appeared. Long-term use of erythromycin was added to his treatment regimen, but the symptoms remained. Methicillin-resistant Staphylococcus aureus (MRSA) was isolated from his sputum in May 1992, and treatment with 6 tablets of TMP-SMZ daily (one tablet included 40 mg of TMP and 200 mg of SMZ), to which MRSA was sensitive, was begun in combination with ciprofloxacin hydrochloride and minocycline. He showed marked improvement and became asymptomatic within several days. He remained free from lower respiratory tract symptoms after cession of antibiotics other than TMP-SMZ. MRSA disap-
peared and only normal habitants were isolated from sputum within a few months. *P. aeruginosa*, however, appeared again in the sputum without exacerbation of the respiratory symptoms. The dose of TMP-SMX was reduced to 3 tablets/day in December 1992. ESR and CRP fell within the respective normal ranges. Arterial blood gas analysis also improved (PaO2, 77.2 Torr; PaCO2, 46.2 Torr; pH 7.390). When TMP-SMZ was reduced to one tablet/day in June 1993, his temperature rose to 38.5°C with an increase of white blood cells and elevation of CRP and ESR, although a chest roentgenogram did not show new consolidation (Fig. 2). The dose of TMP-SMZ was increased to 2 tablets/day and his temperature was reduced. He then continued to take the same dose daily for one year, and no side effects were observed. When the dose of TMP-SMZ was again reduced gradually and stopped in June 1994, he noted fever and an increase in productive cough. TMP-SMZ therapy was restarted and the symptoms disappeared immediately. He has remained free from symptoms on a regimen of one tablet of TMP-SMZ per day without adverse reactions to date.

**Case 2** (Fig. 3)

A 34-year-old female had suffered from abscesses on various regions of her body without pain. She was diagnosed as having hyper IgE syndrome with a serum IgE level of over 10,000 IU/ml when she was 13 years old. She had an operation for a peritoneal abscess at the age of 17 years. She was also...
admitted for treatment of myelitis of the right femur and an abscess on the upper pharynx at 20 and 30 years old. From 1989, when she was 30 years old, she often came to our hospital with respiratory infection and high fever. She was diagnosed as having bronchiectasis and was treated with various antibiotics. She had no history of chronic sinuitis or pulmonary tuberculosis. A chest roentgenogram (Fig. 3) and CT scans showed cystic lesions and bronchial thickening in the right upper lobe and bronchial thickening in both lower lobes. These respiratory symptoms often disturbed her activity in daily life and she was admitted several times over the following years. Methicillin-sensitive Staphylococcus aureus (MSSA) and P. aeruginosa were isolated from sputum. In 1991, MRSA was first detected in sputum and TMP-SMZ was added to the other antibiotics in her treatment regimen. After initiation of TMP-SMZ treatment, the symptoms of respiratory infection were reduced. The dose of TMP-SMZ was reduced and stopped because we had no experience regarding its long-term use and the available drug information emphasized its side effects. On February 9, 1993, she again visited our hospital with fever and productive cough, and she was treated with oral cephalosporin not TMP-SMZ. She developed the above symptoms and then dyspnea appeared within three days. Chest roentgenogram showed patchy infiltration shadows in both lung fields (Fig. 4) and MRSA was isolated from blood. She was diagnosed with adult respiratory distress syndrome accompanied by MRSA sepsis, which was caused by MRSA pneumonia. She recovered after intensive treatment with vancomycin, habekacin, minomycin and TMP-SMZ to which MRSA is sensitive. Subsequently, TMP-SMZ was used at a dose of 4 tablets/day without other antibiotics for one year and 2 tablets/day have been continued as a prophylaxis against further infections. P. aeruginosa was often isolated from sputum, although she has remained free from symptoms of respiratory infection. The level of serum IgE gradually fell to 2,000 IU/ml.
Discussion

A number of studies have shown that TMP-SMZ is an effective agent for treatment of respiratory tract infections (2–4). TMP-SMZ is not, however, considered the drug of first choice, because many other antibiotics have been developed and used for various bacterial infections.

Most *Staphylococcus aureus* strains, regardless of methicillin susceptibility, have shown susceptibility to TMP-SMZ. The Japan Cooperative Clinical Study Group reported that therapy with TMP-SMZ was effective in 86 of 109 patients with *Staphylococcus aureus* infection (5). However, resistance to TMP-SMZ in staphylococci may be rising; it has been reported that 60% of MRSA strains and 15% of MSSA were resistant to TMP-SMZ (6). In the present two cases, TMP-SMZ was used for the treatment of MRSA infection, and MRSA disappeared. *P. aeruginosa* appeared again in the sputum some months later. The rate of respiratory infections, however, was apparently reduced in both patients, and the white blood cell count, ESR and CRP fell to within the respective normal ranges. After cessation of TMP-SMZ therapy respiratory infections recurred in both patients. TMP-SMZ therapy was restarted, and they have remained free of respiratory tract symptoms and signs on low-dose TMP-SMZ treatment for over one year. The beneficial effects of TMP-SMZ are clinically apparent in these two patients with severe bronchiectasis, whose disease could not be controlled with other antibiotics. However, the doses of TMP-SMZ used here were low, and *P. aeruginosa*, which appeared after the use of TMP-SMZ, did not show susceptibility to TMP-SMZ. It is supposed that TMP-SMZ has effects on the respiratory infection other than its bactericidal action.

There were some reports in the 1970’s and 1980’s that TMP-SMZ is effective for long-term use in the treatment of chronic bronchitis and cystic fibrosis (2, 3). More recently, there have also been several reports concerning long-term (over a year) TMP-SMZ regimens for various diseases, and no severe side effects were observed (3, 7–9). Long-term therapy with TMP-SMZ seems to be safe and effective, although the length of the period it may be used without adverse side effects has not been determined.

It was reported that a patient with hyper IgE syndrome showed evident clinical improvement and a decrease in serum IgE level following TMP-SMZ treatment (9, 10). It is thought that TMP-SMZ improves the function of polymorphonuclear leukocytes in addition to having a bacterial effects, although the mechanism of this effect remains unclear (9).

Severe adverse reactions to TMP-SMZ do not occur as often as expected. Most patients in earlier studies were elderly (mean age 81 years) and female, and they developed hematological toxicity within a few weeks of initiation of TMP-SMZ treatment (11, 12). TMP is considered a selective inhibitor of dihydrofolate reductase in bacteria but not in humans. However, minor effects on folate metabolism and some degree of blood dyscrasias were observed in humans (13); its incidence, 2.6 per million at defined daily doses, was not high and 154 cases were reported in Sweden between 1976 and 1985. The mortality rate for patients with bicytopenia was reported as 6%, and 52% for those with tricytopenia (11). Most patients with blood dyscrasias showed improvement when TMP-SMZ therapy was stopped or folic acid treatment started (13).

It is difficult to determine the appropriate dose of TMP-SMZ for individual patients. For simultaneous primary prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmosis in patients infected with HIV, TMP-SMZ administered three times per week (160 mg–800 mg orally twice a day) is an effective and well-tolerated regimen (14), and for the prevention of spontaneous bacterial peritonitis in patients with cirrhosis, one double-strength TMP-SMZ tablet daily, five times a week (Monday through Friday), was efficacious, safe, and cost effective (15). The present two cases have remained free from the symptoms and signs of respiratory tract infections following commencement of treatment with TMP-SMZ.

The Japanese drug directions say that TMP-SMZ must be used only when other antibiotics are not effective. However, the incidence of fetal hematological toxicity (especially tricytopenia) is very low. Most patients who present with blood dyscrasias are over 65 years old, and symptoms appear within several weeks from the initiation of TMP-SMZ therapy. If clinicians are aware of the above side effects and use this drug, TMP-SMZ seems to be safe and effective for patients suffering from repeated high fever and productive cough resistant to various antibiotics.

References


