Case Report

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Successful treatment with clarithromycin and/or tacrolimus for two patients with polymyalgia rheumatica

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Summary **Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease in the elderly. Glucocorticoids (GCs) remain the mainstay of treatment. GC therapy usually dramatically improves the clinical picture, but approximately one-third of patients experience disease recurrence when the dose is reduced. Moreover, long-term use of GCs causes adverse reactions. Macrolide antibiotics have anti-inflammatory action. Several recent studies have reported the successful treatment of rheumatoid arthritis (RA) and PMR treated using clarithromycin (CAM), a macrolide, because of its anti-inflammatory action. Tacrolimus (TAC) has been indicated as a treatment for RA in patients who failed to respond to methotrexate. Recently, a case of RA was successfully treated using CAM and TAC according to one report. Reported here are two cases of PMR treated using CAM and/or TAC. Case 1: A 73-year-old man suffering from PMR was successfully treated with prednisolone (PSL) and CAM. Because his muscle pain disappeared, CAM was discontinued. However, the pain returned after that discontinuation, so CAM was successfully administered again. Case 2: An 83-year-old man suffering from PMR was successfully treated with PSL and CAM. Because muscle pain disappeared, the CAM dosage was halved. The pain returned after the dosage was reduced, so the CAM dosage was successfully resumed and the PSL dosage was reduced. When the PSL dosage was reduced, muscle pain recurred. Because the PSL and CAM dosages were not successfully increased, TAC was also administered and was found to be effective at treating muscle pain. These two cases suggest that CAM and/or TAC are effective at treating PMR.**

Keywords: Polymyalgia rheumatica, clarithromycin, tacrolimus

1. Introduction

Macrolide antibiotics (MACs) such as clarithromycin (CAM) have anti-inflammatory action as well as antibacterial activity. Several recent studies reported the successful treatment of rheumatoid arthritis (RA) (*1*) and polymyalgia rheumatica (PMR) through use of CAM as an anti-inflammatory drug (*2*). A recent study has indicated that tacrolimus (TAC), a Japanese domestic disease-modifying antirheumatic drug, is a treatment for active RA patients who fail to respond to methotrexate (*3*). Recently, a case of RA was successfully treated with CAM and TAC (*4*). Reported here are a case of PMR treated with CAM and a case of PMR treated with CAM and TAC.

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2. Case Reports

2.1. *Case 1*

A 73-year-old man presented with subacute onset of severe muscle pain in his neck, both shoulders, his lower back, and both thighs. Muscle tenderness was noted in all of the areas in question. However, swelling and deformity of joints were not noted. Laboratory results were a white blood cell count (WBC) of 9,090 cells/μL (normal range, 4,000 to 9,800 /μL), a C-reactive protein (CRP) level of 7.14 mg/dL (normal value, < 0.3

mg/dL), an erythrocyte sedimentation rate of 95 mm/h (normal range, 1 to 10 mm/h), a rheumatoid factor concentration of < 15 IU/mL (normal value, < 15 IU/mL), and an antinuclear antibody (ANA) titer of 40× (normal value, < 40×). Tests for myeloperoxidase and proteinase-3 antineutrophil cytoplasmic antibodies were negative. Ultimately, the patient was diagnosed with PMR and treated with prednisolone (PSL) (15 mg/day). According to a previous report (*2*) CAM has anti-inflammatory action, so the current patient was also treated with CAM (400 mg/day). After 1 week of this treatment, muscle pain disappeared, and CRP decreased to 0.20 mg/dL. The PSL dosage was gradually decreased; when PSL was administered at a dosage of 10 mg/day, CAM was discontinued. The PSL dosage was gradually decreased further to 6 mg/day without any muscle pain. The patient was then administered a dosage of 5 mg/day. After 2 weeks of this treatment, muscle pain recurred, and CRP increased to 1.24 mg/dL (first relapse). Instead of increasing the PSL dosage, CAM (400 mg/day) was administered again. Two weeks after restarting CAM treatment, muscle pain disappeared, and CRP decreased to 0.21 mg/dL. CAM was then discontinued again. Two weeks after discontinuing CAM, muscle pain recurred, and CRP increased to 1.98 mg/dL (second relapse). CAM was administered again at a dose of 400 mg/day. Two weeks after restarting CAM treatment, muscle pain disappeared, and CRP decreased to 0.20 mg/dL. For 8 weeks, the patient was successfully treated with PSL (5 mg/day) and CAM (400 mg/day), so the PSL dosage was successfully decreased to 4 mg/day.

2.2. *Case 2*

An 83-year-old man presented with subacute onset of severe muscle pain in his neck, both shoulders, his lower back, his hip girdle, and both thighs. Muscle tenderness was noted in all of the areas in question. However, swelling and deformity of the joints were not noted. Laboratory results were a WBC of 7,180 cells/μL, a CRP level of 11.59 mg/dL, an anti-cyclic citrullinated peptide antibody titer of 0.6 U/mL (normal value, < 4.5 U/mL), and an ANA titer of 40×. Tests for myeloperoxidase and proteinase-3 antineutrophil cytoplasmic antibodies were negative. Ultimately, the patient was diagnosed with PMR. The PSL dosage needed to be minimized in light of osteoporosis and hyperglycemia, so the patient was treated with PSL at a dosage of 10 mg/day instead of 15 mg/day. According to a previous report (*2*) CAM has anti-inflammatory action, so the current patient was also treated with CAM (400 mg/day). One week after this treatment, muscle pain disappeared, and CRP decreased to 0.67 mg/dL. The PSL dosage was gradually decreased to 7 mg/day without any muscle pain. Since muscle pain disappeared, the CAM dosage was decreased to 200 mg/day while the PSL dosage was 6 mg/day. Two weeks after starting CAM (200 mg/day) treatment, muscle pain recurred, and CRP increased to 1.31 mg/dL (first relapse). Treatment with CAM (400 mg/day) was therefore restarted. Four weeks after resuming CAM (400 mg/day) treatment, muscle pain disappeared, and CRP decreased to 0.21 mg/dL. The PSL dosage was gradually decreased to 4 mg/day. The patient was then treated with PSL (3 mg/day) and CAM (400 mg/day). Four weeks after starting this treatment, slight muscle pain developed but this was tolerated by the patient. Eight weeks after starting this treatment, muscle pain worsened, and CRP increased to 12.97 mg/dL (second relapse). The PSL dosage was increased to 10 mg/day and the CAM dosage was increased to 800 mg/day. For 1 week, this treatment alleviated muscle pain to a certain extent, but CRP remained high (7.90-9.04 mg/dL); therefore, the PSL dosage was successfully increased to 15 mg/day while the CAM dosage was decreased to 400 mg/day. The PSL dosage was gradually decreased to 10 mg/day without muscle pain. Although muscle pain substantially disappeared, CRP remained high at approximately 1.9 mg/mL while the patient received PSL (10 mg/day) and CAM (400 mg/day). The PSL dosage could not be decreased any further for fear of recurrent muscle pain, so TAC (0.5 mg/day) was also administered. One week after the addition of TAC treatment, CRP decreased to 0.55 mg/dL. The trough level of TAC was 3.3 ng/mL. The PSL dosage was gradually decreased to 4 mg/day, and CRP remained at 0.30 mg/dL without recurrent muscle pain.

3. Discussion

Glucocorticoids (GCs) are the mainstay of PMR treatment. GC therapy usually dramatically improves the clinical picture within a few days, but approximately one-third of patients experience disease recurrence when the dose is reduced. Long-term use of GC causes adverse reactions in up to 60% patients.

MACs have anti-inflammatory action as well as antibacterial activity. MACs exhibit anti-inflammatory action by affecting several pathways of the inflammatory process, such as the production of proinflammatory cytokines. In fact, CAM inhibits the production of interleukin-6 (IL-6) (*5*), which is associated with the clinical features of RA. Similarly, TAC has been reported to suppress the production of IL-6 (*6*). Serum IL-6 levels are reported to increase and are closely associated with disease activity in PMR (*7*), so the efficacy of treatment with CAM and/or TAC in the current cases might be due to the anti-inflammatory action of CAM and/or TAC with regard to the suppression of IL-6 production. In Case 1, CAM was effective in treating both relapses. In Case 2, however, CAM was effective in treating the first relapse but not in treating the second relapse. This necessitated

the addition of TAC. CAM was ineffective in treating the second relapse in Case 2 presumably because inflammation was more severe during the second relapse than during the first relapse or because long-term use of CAM induced drug tolerance. In light of the current findings, treatment with CAM and/or TAC for PMR was effective. Moreover, TAC appeared to be superior to CAM in terms of anti-inflammatory action. Studies have noted pharmacokinetic interaction between CAM and TAC since CAM causes an increase in the concentration of TAC in the blood by inhibiting its metabolism (*8*). Research has shown that TAC is primarily metabolized by cytochrome P450 (CYP)3A; when TAC is administered orally, its concentration in the blood tends to widely vary between individuals. CAM is a potent CYP3A inhibitor, so combined administration of both CAM and TAC leads to pharmacokinetic interactions. As a result, CAM increases the concentration of TAC in the blood by inhibiting its TAC metabolism via inhibition of CYP3A (*8*). Recent cases of lupus nephritis and adult-onset Still's disease were successfully treated using TAC; in those cases, CAM was administered in order to increase the concentration of TAC in the blood (*9,10*). Suzuki et al. measured the concentration of TAC in the blood of patients with RA, and they found that the concentration of TAC in the blood was 2.96 ng/mL in patients receiving a dose of 1 mg/day, 4.29 ng/mL in patients receiving a dose of 2 mg/day, and 8.32 ng/mL in patients receiving a dose of 3 mg/day (*11*). However, the concentration varied widely in individual patients in those three groups. The concentration of TAC (0.5 mg/day) in the blood was 3.3 ng/mL in Case 2, so pharmacokinetic interaction between CAM and TAC presumably increased the concentration of TAC in the blood, resulting in a reduction in the dose of TAC, which is quite expensive. Therefore, treatment of refractory PMR with CAM and TAC, as in the second relapse in Case 2, may be recommended from an economic perspective. PMR is one of the most common chronic inflammatory syndromes in elderly individuals. Elderly patients tend to suffer from chronic diseases that are exacerbated by the use of GCs, such as diabetes mellitus, osteoporosis, and hypertension, so treatment with CAM and/or TAC may be helpful in reducing conventional GS dosages.

Because only two cases have been reported here, more research is necessary before this treatment with CAM and/or TAC can be adopted on a wider basis.

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