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Letter to the Editor

Successful Treatment of Polymyalgia Rheumatica with Prednisolone in Combination with Clarithromycin and Tacrolimus

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Polymyalgia rheumatic (PMR) is an inflammatory rheumatic disease affecting the elderly population. Glucocorticoids (GCs) remain the mainstay of treatment. GC therapy usually dramatically improves the clinical presentation. But approximately one third of patients experience disease recurrence when the dose is reduced. Methotrexate (MTX) is considered a promising agent in the treatment of PMR, and MTX in addition to GC reduces the time for discontinuing GCs, the incidence of relapse, and the cumulative GC dose. The use of interleukin (IL)-6 receptor inhibitor tocilizumab as monotherapy and in combination with GC was reported to be effective and safe to treat patients with PMR [1,2]. Tacrolimus (TAC) has been recently indicated as a treatment for active rheumatoid arthritis (RA) with inadequate response to MTX. Macrolide antibiotics (MACs), such as clarithromycin (CAM), provide not only antibacterial activity but also anti-inflammatory effects. Several recent studies reported the successful treatment of RA [2] and PMR [3] using CAM as an anti-inflammatory agent. Recently, a successful case of RA treated with TAC and CAM was reported [4]. Here we report a case of PMR treated with TAC and CAM.

A 73-year-old woman presented with stiffness and muscle pain in her neck, shoulders, lower back, and hip girdle. These symptoms gradually worsened over 10 days. Physical examination revealed muscle tenderness in these areas. There was neither swelling nor deformity of the joints. Laboratory findings were as follows: white blood cell count, 9,620 / μL (neutrophils, 70.6%; eosinophils, 0.90%; monocytes, 6.9%; lymphocytes, 21.2%); creatine phosphokinase, 121 U/L (normal range, 50～210 U/L); C-reactive protein (CRP), 1.91 mg/dL (normal value, ＜0.30 mg/dL); erythrocyte sedimentation rate, 29 mm/h (normal range, 3～15 mm/h); rheumatoid factor (RF), 5 IU/L (normal value, ＜15.0 IU/L); anti-cyclic citrullinated peptide antibody, 0.5 U/mL (normal value, ＜4.5 U/mL); and antinuclear antibody titer, ×40 (normal value, less than ×40). No abnormal findings suggestive of infection could be found in the systemic survey, including the chest roentgenogram and urinalysis. Finally, the patient was diagnosed with PMR according to the classification criteria [5]. Because her muscle pain was not so severe and she was suffering from diabetes mellitus, she was treated with CAM (400 mg/d), in consideration of its anti-inflammatory effects [3], as an alternative to prednisolone (PSL). One week after initiating CAM treatment, muscle pain improved only slightly, although CRP decreased to 1.42 mg/dL (Figure 1). Therefore, PSL (5 mg/d) was added to the CAM treatment. Two weeks after PSL in combination with CAM treatment, muscle pain improved and CRP decreased to 0.20 mg/dL. CAM was ceased in 5 weeks. The PSL dosage was gradually decreased to 3 mg/d over 2 months. Two weeks after PSL (3 mg/d) monotherapy, muscle pain recurred and CRP increased to 0.68 mg/dL. CAM (400 mg/d) was added to PSL (3 mg/d). Two weeks after the add-on CAM treatment, muscle pain improved moderately, and CRP decreased to 0.46 mg/dL. But 6 weeks after add-on CAM treatment, muscle pain became exacerbated, and CRP increased to 0.82 mg/dL. The patient refused to receive MTX because it is a sort of chemo-

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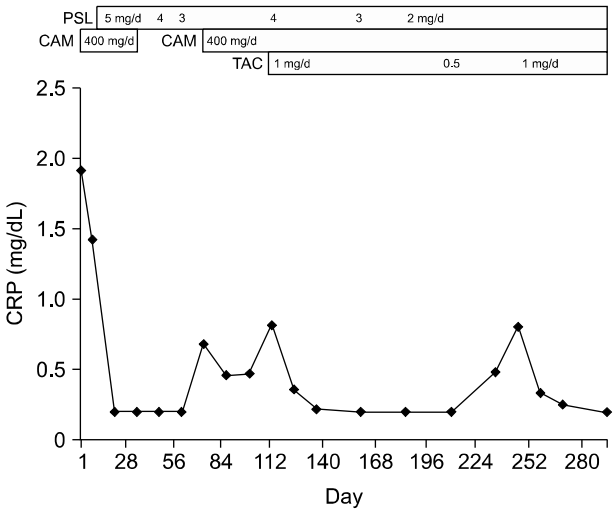

Figure 1. The laboratory data and prescribed agents on clinical days. PSL: prednisolone, CAM: clarithromycin, TAC: tacrolimus, CRP: C-reactive protein.

therapy agent. At the same time, she could not afford an IL-6-receptor inhibitor owing to its high cost. Therefore, the PSL dosage was increased to 4 mg/d. At the same time, TAC (1 mg/d) was added. Because TAC blood concentrations are known to be affected by the fat content of food, we advised the patient to take TAC 2 hours before supper in order to keep the TAC at a fixed blood concentration. We regarded the optimal trough levels of TAC as 5.0～10.0 ng/mL. Four weeks after PSL (4 mg/d) in combination with CAM (400 mg/d) and TAC (1 mg/d) treatment, muscle pain improved, and CRP decreased to 0.20 mg/dL. The trough levels of TAC (1 mg/d) were 10.2 ng/mL. The PSL dosage was gradually decreased to 2 mg/d over 3 months without recurrent muscle pain, and CRP remained at 0.20 mg/dL. The TAC dosage was also decreased to 0.5 mg/d in 4 months. Six weeks after decreasing the TAC dosage, muscle pain recurred, and CRP increased to 0.81 mg/dL; therefore, the TAC dosage was increased again to 1 mg/d. Four weeks after resuming TAC (1 mg/d) treatment, muscle pain improved, and CRP decreased to 0.25 mg/dL.

TAC has been reported to suppress the production of IL-6 [6]. Similarly, MACs have been shown to affect several pathways of the inflammatory process, such as the production of pro-inflammatory cytokines, including IL-6 [7]. Because it was reported that serum IL-6 levels increased and showed the strongest association with disease activity in PMR [8], the efficacy of treatment with TAC and CAM in the present case might be due to anti-inflammatory effects caused by their suppression of IL-6 production. Compared with that of the previous report [3], the efficacy of CAM in the clinical course of the present case was thought not to be sufficiently satisfactory. In order to suppress the PMR activity further, TAC was successfully added. CAM is known to suppress TAC metabolism by inhibiting cytochrome P450 3A4, increasing TAC blood concentrations. Suzuki et al. [9] measured TAC blood concentrations in RA patients. According to them, the trough levels of TAC in the 1, 2, and 3 mg/d groups were 2.96, 4.29, and 8.32 ng/mL, respectively, although these levels had a wide range amongst the individuals within the groups. In the present case, because the trough levels of TAC (1 mg/d) were 10.2 ng/mL, we speculate that CAM increased TAC blood concentrations, resulting in the reduction of expensive TAC dosages. In general, initial therapy for PMR is PSL (15～20 mg/d); however, PSL (5 mg/d) in combination with CAM was successfully initiated in the present case. Based on these findings, PSL in combination with CAM and TAC treatment was thought to be effective for PMR. Moreover, CAM could reduce the required PSL and TAC dosages. Because only one case has been reported, more research is necessary before this treatment can be adopted on a wider basis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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