

Successful treatment with clarithromycin for patients with polymyalgia rheumatica

Masashi Ohe¹ and Toshiyuki Bohgaki²

¹Department of General Medicine, Hokkaido Social Insurance Hospital, Sapporo; ²Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

To the Editor,

Macrolide antibiotics (Macs) such as erythromycin and clarithromycin (CAM) have anti-inflammatory effects in addition to antibacterial activity. Using these anti-inflammatory effects, Macs have successfully treated pathologies such as diffuse panbronchiolitis and sinusitis. Similarly, several recent studies have described the successful treatment of rheumatoid arthritis (RA) using CAM [1]. Polymyalgia rheumatica (PMR) is an inflammatory disease in which elevated proinflammatory cytokines such as tumor necrosis factor (TNF)- α and interleukin (IL)-6 are associated with clinical features, as is often the case with RA. Here, we report three cases of PMR treated successfully using CAM based on its anti-inflammatory effects suppressing TNF- α and IL-6 (Table 1) [2].

A 73-year-old woman was referred with subacute onset of severe pain in her neck, shoulders, arms, lower back, hip girdle, and thighs. Muscle tenderness was observed in these areas. However, neither swelling nor deformity of the joints was found. The laboratory findings were as follows: white blood cell count 6,140/ μ L, C-reactive protein (CRP) 7.17 mg/dL, erythrocyte sedimentation rate 58 mm/hr, rheumatoid factor 8 IU/mL (normal range, < 15), anticyclic citrullinated peptide

antibody testing 2.5 U/mL (normal range, < 4.5), and antinuclear antibody titer $\times$ 40. Negative results were obtained for myeloperoxidase and proteinase-3 antineutrophil cytoplasmic antibodies. Ultimately, the patient was diagnosed with PMR. As she had uncontrolled diabetes mellitus, she was treated using CAM (400 mg/day) as an alternative to glucocorticoid (GC) after obtaining informed consent to start prednisolone (PSL) treatment immediately after any further exacerbation of PMR or after achieving control of diabetes mellitus. Two weeks later, her symptoms had improved and the CRP had decreased from 7.17 to 0.2 mg/dL. Since the symptoms had improved, the CAM was discontinued at her request. Two weeks after stopping the CAM, the symptoms recurred and the CRP increased to 2.69 mg/dL. Treatment with CAM was restarted at 400 mg/day. Two weeks after resuming treatment, the symptoms had again improved and the CRP had decreased to 0.34 mg/dL.

A 78-year-old woman with a 2-year history of PMR, which had been controlled by PSL (5 mg/day), presented with pain in the shoulders, hip girdle, and thighs and the CRP level had increased from 0.2 to 3.77 mg/dL. The symptoms had appeared after reducing the PSL dosage from 5 to 4 mg/day over 2 months to avoid an exacer-

Received: January 20, 2014
Revised : February 26, 2014
Accepted: March 13, 2014

Correspondence to
Masashi Ohe, M.D.

Department of General Medicine, Hokkaido Social Insurance Hospital, 1-8-3-18 Nakanoshima, Toyohira-ku, Sapporo 062-8618, Japan
Tel: +81-11-831-5151
Fax: +81-11-821-3851
E-mail: masshi@isis.ocn.ne.jp

Table 1. Patient characteristics

Characteristic	Patient no.		
	1	2	3
Age, yr	73	78	77
Sex	Female	Female	Male
ESR, mm/hr	58	-	-
CPR, mg/dL	7.17	3.77	0.99
Previous treatment	-	PSL 4 mg/day	PSL 10 mg/day
CAM, mg/day	400	400	400
Therapeutic response	Good	Good	Good

ESR, erythrocyte sedimentation rate; CPR, C-reactive protein; PSL, prednisolone; CAM, clarithromycin.

bation of osteoporosis. A diagnosis of exacerbation of PMR was made. She was treated with CAM (400 mg/day) in combination with PSL (4 mg/day), after obtaining informed consent to start an increased dosage of PSL immediately after any further exacerbation of the PMR. Four weeks after starting the CAM, her symptoms had improved, with the CRP decreasing to 0.33 mg/dL.

A 77-year-old man with a 2-month history of PMR, which had been controlled by PSL (12.5 mg/day), presented with stiffness in the shoulders and lower back and an increase in CRP from 0.2 to 0.99 mg/dL after reducing the PSL dosage from 12.5 to 10 mg/day over 2 weeks. As an alternative to reincreasing the dosage of PSL, CAM (400 mg/day) was added because of its anti-inflammatory effects after obtaining informed consent to start an increased dosage of PSL immediately after any further exacerbation of the PMR. Two weeks later, his symptoms had improved with the CRP decreasing to 0.2 mg/dL.

The etiology and pathophysiology of PMR remain unclear. However, PMR is sometimes associated with neoplastic, other rheumatic, or infectious diseases. Some cases of PMR have been reported with or without remitting seronegative symmetrical synovitis with pitting edema after *Mycoplasma pneumoniae* infection [3]. In that report, the patients were given PSL, not antibiotics. Antibiotics were not administered because the mycoplasma infection had merely triggered the PMR. Therefore, even if an infection sensitive to CAM was involved at the onset of PMR in case 1, the effectiveness of the CAM was thought to have been derived

from its anti-inflammatory effects, and not from its antibacterial activity.

Regarding the treatment of PMR, GC remains the mainstay. GC therapy usually dramatically improves the clinical picture within a few days. Nevertheless, about one-third of patients experience disease recurrence when the dose is reduced. Long-term use of GC induces side effects, which occur in up to 60% of patients. Methotrexate (MTX) is considered a promising agent and MTX in addition to GC reduces the time for discontinuing GCs, the incidence of relapse, and the cumulative GC dose. Alternatively, TNF blocking agents were found not to be sufficiently effective [4].

Apart from their antibacterial activity, Macs exhibit a broad spectrum of pharmacological effects, including anti-inflammatory activity. Macs have been shown to affect several pathways of the inflammatory process, such as the migration of neutrophils, the oxidative burst in phagocytes, and the production of proinflammatory cytokines [1]. Via their antibacterial activity, Macs also greatly influence anti-inflammatory activity. For instance, Macs are active against periodontopathic bacteria, which are powerful stimulators of TNF- α and other proinflammatory cytokines in humans [1]. Since it was reported that the serum levels of both TNF- α and IL-6 were elevated in PMR [5], the effectiveness of CAM for PMR in our cases was thought to be derived from its anti-inflammatory effects, including suppressing the above-mentioned proinflammatory cytokine production.

Two of our patients who had already received PSL were treated with CAM. Since Macs have steroid-spar-

ing effects via their influence on corticosteroid metabolism, not only the above-mentioned anti-inflammatory effects but also their steroid-sparing effects might have resulted in the improved signs and symptoms.

PMR is one of the most common chronic inflammatory diseases in the elderly. As elderly patients tend to suffer from chronic diseases that are exacerbated by the use of GCs, such as diabetes mellitus, osteoporosis, and hypertension, CAM monotherapy and CAM add-on therapy might represent useful options for elderly patients with PMR.

Given that only three cases were reported here, more research is necessary before CAM therapy can be adopted widely.

Keywords: Polymyalgia rheumatica; Clarithromycin

Conflict of interest

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

REFERENCES

1. Ogrendik M. Effects of clarithromycin in patients with active rheumatoid arthritis. *Curr Med Res Opin* 2007;23:515-522.
2. Khan AA, Slifer TR, Araujo FG, Remington JS. Effect of clarithromycin and azithromycin on production of cytokines by human monocytes. *Int J Antimicrob Agents* 1999;11:121-132.
3. Matsuda M, Shimojima Y, Gono T, et al. Remitting seronegative symmetrical synovitis with pitting oedema/polymyalgia rheumatica after infection with *Mycoplasma pneumoniae*. *Ann Rheum Dis* 2005;64:1797-1798.
4. Soriano A, Landolfi R, Manna R. Polymyalgia rheumatica in 2011. *Best Pract Res Clin Rheumatol* 2012;26:91-104.
5. Cutolo M, Montecucco CM, Cavagna L, et al. Serum cytokines and steroidal hormones in polymyalgia rheumatica and elderly-onset rheumatoid arthritis. *Ann Rheum Dis* 2006;65:1438-1443.