Add-on Clarithromycin and Tacrolimus Treatment for Rheumatoid Arthritis

Masashi Ohe
Department of General Medicine, JCHO Hokkaido Hospital, Sapporo, Japan

Macrolide antibiotics such as clarithromycin (CAM) exhibit not only anti-bacterial activity but also anti-inflammatory effects. Several recent studies have reported the successful treatment of rheumatoid arthritis (RA) using CAM as an anti-inflammatory drug [1]. On the other hand, tacrolimus (TAC), a Japanese domestic disease-modifying anti-rheumatic drug, has been recently indicated as a treatment for active RA with an inadequate response to methotrexate [2]. With regards to the pharmacokinetic interaction between CAM and TAC, studies have shown that CAM causes an increase of TAC concentration in blood by suppressing TAC metabolism [3]. Research has shown that TAC is primarily metabolized by cytochrome P450 (CYP)3A, and when TAC is administered orally, blood concentrations tend to widely vary between individuals. As CAM is a potent CYP3A inhibitor, co-administration of both CAM and TAC leads to pharmacokinetic interactions. As a result, CAM suppresses TAC metabolism by inhibiting CYP3A; thus, the trough levels of TAC increase. Recently, a successful case of lupus nephritis treated using TAC was reported in which CAM was administered for the purpose of increasing TAC blood concentrations [4]. Herein, we report a case of uncontrolled RA treated using these two drugs in consideration of the above-mentioned anti-rheumatic effects and pharmacokinetic interaction.

A 64-year-old woman suffering from RA presented with exacerbation of arthralgia and/or articular swellings in the wrist, hand, and knee joints. At 57 years of age, she was diagnosed with organizing pneumonia (OP), an interstitial pneumonia, which was diagnosed by video-assisted thoracoscopic surgery and gradually improved considerably without any treatment. Three months after the diagnosis of OP, she complained of arthralgia and articular swellings. She was diagnosed with RA; therefore, OP was thought to be associated with RA. We evaluated the RA activity using disease activity score (DAS28-C-reactive protein (CRP)). With regards to disease activity, DAS28-CRP over 4.1 indicates high disease activity, whereas that below 2.7 indicates low disease activity. Especially, DAS28-CRP below 2.3 indicates remission. DAS28-CRP between 4.1 and 2.7 indicates moderate disease activity [5]. Because her DAS28-CRP was 4.46, she was unsuccessfully treated with a combination of salazosulfapyridine (SASP) (1 g/d) and etodolac (ETD) (400 mg/d). The patient decided to receive neither methotrexate nor leflunomide because several cases of interstitial pneumonia caused by these two drugs have been reported. Similarly, owing to their high costs, she could receive neither tumor necrosis factor-α blocking agents nor an interleukin-6 receptor inhibitor. As an alternative, prednisolone (PSL) (5 mg/d) was successfully added to the above-mentioned treatment. The PSL dosage was gradually decreased to 3 mg/d without RA exacerbation. Approximately 6 months after beginning the PSL treatment, OP showed almost complete improvement on PSL (3 mg/d). For almost 7 years, RA had been largely controlled using SASP in combination with ETD and PSL (3 mg/d), with low disease activity. On this visit, DAS28-CRP increased to 3.62. Because the PSL dosage could not be increased any further owing to the fear of osteoporosis, CAM (400 mg/d) was added to SASP in combination with ETD and PSL, in expectation of its anti-inflammatory effects on RA [1]. Six months after starting this treatment,
arthralgia and articular swellings, except for those of knee joints, largely improved. DAS28-CRP decreased to 3.10. Because arthralgia and articular swellings of knee joints did not improve sufficiently, TAC (2 mg/d) was added to the treatment. We regarded the optimal trough levels of TAC as 4.0~8.0 ng/mL. Although the patient’s trough levels were 3.8 ng/mL, 4 months after starting this treatment, arthralgia and articular swellings including those of knee joints, almost completely improved, as DAS28-CRP decreased to 2.16. Furthermore, there was no recurrence of OP before and after the add-on CAM and TAC treatment.

As stated earlier, macrolides exhibit anti-inflammatory effects; they have been shown to affect several pathways of the inflammatory process, such as the production of pro-inflammatory cytokines. In fact, CAM inhibits the production of tumor necrosis factor-α and interleukin-6, which are known to be associated with clinical features of RA. Saviola et al. [1] reported that CAM (500 mg twice a day for the first 10 days, followed by 250 mg twice a day for the long term) could be beneficial in RA patients who are not responsive to, or cannot tolerate, disease-modifying anti-rheumatic drugs. In the present case, add-on CAM treatment proved effective to a certain extent; however, the RA activity was not completely suppressed. In order to suppress the RA activity further, TAC (2 mg/d) was successfully added. Based on these findings and including the above-mentioned pharmacokinetic interaction between CAM and TAC, the efficacy of CAM as an add-on treatment with TAC, might be partly associated with its anti-inflammatory effects. We believe that this pharmacokinetic interaction increases TAC blood concentrations, resulting in the reduction of expensive TAC dosages. To conclude, we suggest that physicians consider add-on CAM and TAC treatment when existing anti-rheumatic drugs show no effect on RA.

CONFLICT OF INTEREST

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

REFERENCES