Add-on Clarithromycin and Tacrolimus Treatment for Rheumatoid Arthritis

Romatoid Artrit için Tedaviye Eklenen Klaritromisin ve Takrolimus

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ABSTRACT

A 67-year-old woman suffering from rheumatoid arthritis (RA) presented with gradual exacerbation of arthralgia and/or articular swellings. She was diagnosed with RA at 62 years of age and successfully treated using methotrexate (MTX) in combination with loxonin (LOX). Three months after this treatment, cytopenia occurred as a side effect of MTX; therefore, MTX was stopped. Thereafter, RA had been largely controlled using salazosulfapyridine in combination with prednisolone and LOX for almost 4 years. On this visit, because RA became worse, clarithromycin (CAM) was added in expectation of its anti-inflammatory effects on RA. CAM treatment was effective for RA, to a certain extent; however, the RA activity was not sufficiently suppressed. In order to suppress the RA activity further, tacrolimus (TAC), an armament in the treatment for active RA in Japan, was added. Three months after initiating TAC treatment, the RA activity was considerably suppressed. This case shows that physicians should consider add-on CAM and TAC treatment when existing ant-rheumatic agents show little effects on RA.

Key Words: Rheumatoid arthritis, clarithromycin, tacrolimus

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ÖZET

Romatoid artrit (RA) hastası olan 67 yaşında bir kadın hasta artralji ve / veya artiküler şişliklerin giderek alevlenmesiyle başvurdu. Hastaya 62 yaşında RA tanısı kondu ve loxonin (LOX) ile kombine halinde metotreksat (MTX) kullanılarak başarıyla tedavi edildi. Bu tedaviden üç ay sonra, MTX'in bir yan etkisi olarak sitopeni meydana geldi, bu nedenle, MTX tedavisi sonlandırıldı. Daha sonra RA, 4 yıl süreyle prednizolon ve LOX ile kombine halde büyük ölçüde salazosülfapiridin kullanılarak kontrol edilmiştir. Bu başvuruda, RA daha kötü hale geldiği için, RA üzerindeki anti-inflamatuar etkileri beklentisiyle tedaviye klaritromisin (CAM) eklenmiştir. CAM tedavisi RA için belli bir ölçüde etkiliydi; bununla birlikte, RA aktivitesi yeterince baskılanamamıştır. RA aktivitesini daha da baskılamak için, Japonya'da aktif RA tedavisi için güçlü bir silah olan takrolimus (TAC) eklenmiştir. TAC tedavisini başlattıktan üç ay sonra, RA aktivitesi önemli ölçüde baskılanmıştır. Bu vaka, hekimlerin mevcut anti-inflamatuar ajanların RA üzerinde çok az etki gösterdiği durumlarda ek CAM ve TAC tedavisini düşünmeleri gerektiğini göstermektedir.

Anahtar Sözcükler: Romatoid artrit, klaritromisin, takrolimus

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INTRODUCTION

Macrolide antibiotics (MACs) such as clarithromycin (CAM) provide 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]. In Japan, tacrolimus (TAC) has been an armament in the treatment for active RA with an inadequate response to methotrexate. We have reported a successful case of uncontrolled RA using CAM and TAC [2]. Herein, we report another case of uncontrolled RA using these two drugs.

CASE REPORT

A 67-year-old woman suffering from RA presented with gradual exacerbation of arthralgia and/or articular swellings in the wrist, hand and knee joints over 3 months. She was diagnosed with RA at 62 years of age and successfully treated using methotrexate (MTX) (6 mg/week) in combination with loxonin (LOX) (180 mg/day). Three months after this treatment, cytopenia occurred as a side effect of MTX; therefore, MTX was stopped. As an alternative, salazosulfapyridine (SASP) (1 g/day) and PSL (5 mg/day) were added. For almost 4 years, RA had been largely controlled using SASP in combination with PSL and LOX.

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We evaluated RA activity, taking advantage of disease activity score (DAS)28-C-reactive protein (CRP). The DAS28-CRP considers 28 tender and swollen joint counts, general health (GH; patient assessment of disease activity using a 100 mm visual analogue scale with 0=best, 100=worst), plus levels of CRP (mg/L). DAS28 values are calculated as follows: DAS28-CRP=0.56 $\sqrt{}$ (TJC28)+0.28 $\sqrt{}$ (SJC28)+0.014GH+0.36ln(CRP+1)+0.96, where TJC=tender joint count and SJC=swollen joint count. Regarding disease activity, DAS28-CRP over 4.1 indicates high disease activity, whereas DAS28-CRP below 2.7 indicates low disease activity and below 2.3 indicates remission. DAS28-CRP between 4.1 and 2.7 indicates moderate disease activity [3]. On this visit, DAS28-CRP was 3.90. The patient could not afford tumor necrosis factor (TNF)-α agents or an interleukin (IL)-6 receptor inhibitor owing to their high costs. As an alternative, CAM (400 mg/day) was added in expectation of its anti-inflammatory effects on RA. Three months after starting add-on CAM treatment, DAS-CRP decreased to 2.95, although arthralgia did not improve sufficiently. Therefore, TAC (1.5 mg/day) was added. Because TAC blood concentrations are known to be affected by the fat content of foods, 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 4.0－8.0 ng/mL. Three months after initiating TAC treatment, her arthralgia and articular swellings improved considerably, and DAS28-CRP decreased to 2.44. The patient's trough levels of TAC were 4.4 ng/mL.

DISCUSSION

Regarding anti-inflammatory effects, CAM has been shown to inhibit the productions of TNF-α and IL-6 associated with RA [4]. Ogrendik reported that treatment with CAM at 500 mg/day for 6 months improved the signs and symptoms in patients with early active RA [1]. TAC has been also reported to suppress the production of TNF-α and IL-6 [5]. Based on these facts and our previous report, the efficacy of treatment with CAM and TAC in the present case might be due to anti-inflammatory effects caused by their suppression of TNF-α and IL-6 production. Regarding the pharmacokinetic interaction between CAM and TAC, CAM is known to suppress TAC metabolism by inhibiting cytochrome P450 3A4, increasing TAC blood concentrations and reducing expensive TAC dosage. However, repeated drug monitoring of TAC is required to prevent adverse reactions. To conclude, physicians should consider add-on CAM and TAC treatment when existing ant-rheumatic agents show little effects on RA.

Conflict of interest

No conflict of interest was declared by the authors.

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