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[Original Article]

EFFECT OF ADDITIONAL ADMINISTRATION OF TACROLIMUS IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH BIOLOGICS

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Abstract :

Objective : To explore the effect of additional administration of tacrolimus to rheumatoid arthritis patients treated with biologics, in whom the effect of biologics is unsatisfactory.

Methods : Tacrolimus was administered if the effect of biologics was unsatisfactory for 24 weeks at least in terms of laboratory data or DAS28 level : ESR, CRP level and DAS28 level were not below 15 mm/h, 0.2 mg/dl or 2.6, respectively.

Results : Tacrolimus administered in addition to biologics was significantly effective for suppressing the activity of rheumatoid arthritis in our study. The significant effect of tacrolimus appeared at the 4th week. The effect of tacrolimus achieved quite significant level at the 54th week ($p < 0.0001$).

Conclusion : Tacrolimus may be a promising candidate to suppress the disease activity of rheumatoid arthritis refractory to the conventional treatment with biologics.

Key words : biologics, coadministration, rheumatoid arthritis, tacrolimus

INTRODUCTION

T-cell activation is critical to the onset and perpetuation of rheumatoid arthritis (RA)¹. Tacrolimus (Tac) exerts its immunosuppressive effects by inhibiting of calcineurin, leading to interference with T-cell activation and proliferation². As T-cell activation plays a major role in the pathogenesis of RA, there has been interest in the use of Tac for the treatment of RA³. Tac was approved in Japan for the treatment of RA in 2005.

There are some patients with RA treated with biologics, in whom the effect of biologics is unsatisfactory. We explored the effect of additional administration of Tac to patients treated with biologics, in whom the effect of biologics is unsatisfactory.

MATERIALS AND METHODS

Patients were enrolled in the study if they met

the American College of Rheumatology 1987 criteria⁴. Disease activity and clinical response were evaluated on the basis of DAS28 (disease activity score of 28 joints) and EULAR (European League Against Rheumatism) response criteria^{5,6}, respectively. Methotrexate (MTX) was administered up to 8 mg/week. The approved MTX dose is up to 8 mg/week in Japan. Biologics such as infliximab or etanercept were administered in accordance with the instructions file attached to these medicines.

If the effect of biologics was unsatisfactory for 24 weeks at least in terms of laboratory data or DAS28 level : ESR, CRP level or DAS28 level were not below 15 mm/h, 0.2 mg/dl or 2.6, respectively, we considered to coadministrate Tac to the biologics. The starting dose was 1 mg/day once daily after dinner, then the dose was increased up to 3 mg. To avoid side effects such as infection and gastrointestinal symptoms, the dose of Tac was kept as low as possible.

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The patients visited our clinic every 4 weeks, and the observation period to determine the effect of the additional administration of Tac on the biologic treatment was at least 12 weeks, and the observation period was extended up to 54 weeks if the additional administration of Tac was effective.

Data were expressed as the mean \pm standard deviation. Data obtained at a specified time were compared with those obtained at baseline or other times using the Wilcoxon signed-rank test. The significance level was $p < 0.05$.

RESULTS

The results on the effect of additional administration of Tac in patients with RA treated with biologics are shown in Table 1. Sixteen infliximab-treated patients and 12 etanercept-treated patients were enrolled in this study. The mean doses of MTX administered to the patients treated with infliximab and those with etanercept were 7.6(4~8) and 5.0(0~8) mg, respectively. The mean doses of Tac administered to the patients treated with infliximab and those with etanercept were 1.56(1~2) and 1.33(1~2) mg, respectively.

Table 1. Baseline characteristics of patients treated with combination of biologics and tacrolimus

	sex	age	Steinbrocker stage	Steinbrocker class	dose of MTX [§] (mg)	final dose of Tacrolimus (mg)
16 patients treated with IFX [†]	F : M=12 : 4	61.2	III	2.1	7.6(4~8)	1.56(1~2)
12 patients treated with ETN [‡]	F : M=8 : 4	66.3	III	2.2	5.0(0~8)	1.33(1~2)

Data are expressed as mean.

[†]IFX, infliximab ; ETN, etanercept

[§]MTX, methotrexate

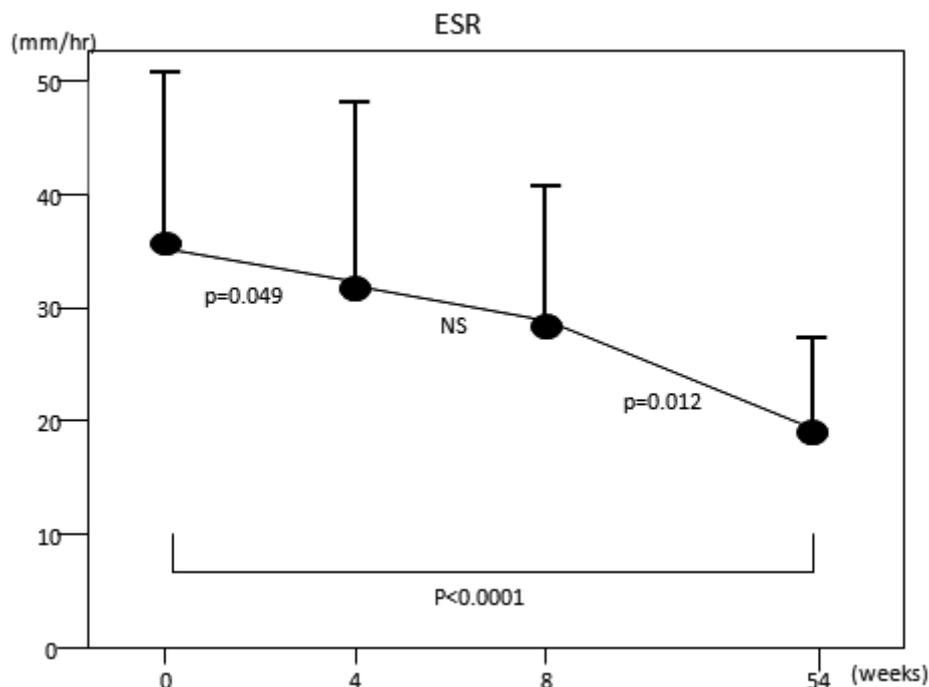


Fig. 1. ESR levels in the first three visits (0, 4, 8th week), and that of 54th week.

ESR level significantly decreased from 37 ± 17 to 32 ± 18 at the 4th week ($p=0.049$). However, there was no significant difference between ESR level of the 4th week and that of the 8th week.

ESR level significantly decreased from 29 ± 16 at 8th week to 18 ± 12 at 54th week ($p=0.012$).

ESR level significantly decreased from week 0 to 54th week ($p < 0.0001$).

Data are expressed as mean \pm SD.

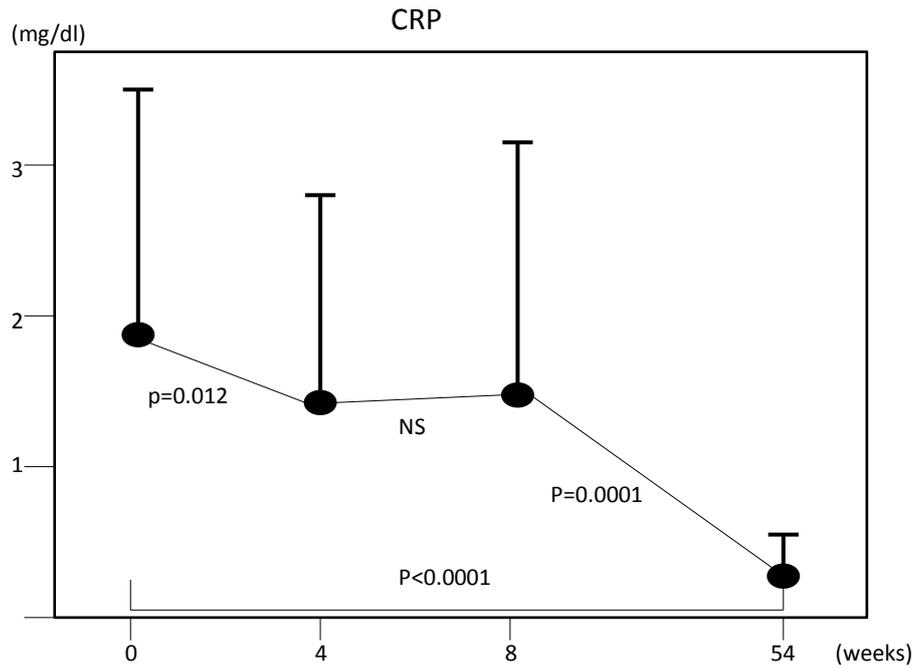


Fig. 2. CRP levels in the first three visits (0, 4, 8th week), and that at 54th week. CRP level significantly decreased from 1.9 ± 1.5 to 1.4 ± 1.5 at the 4th week ($p=0.012$). However, there was no significant difference between CRP level of 4th week and that of the 8th week. CRP level significantly decreased from 1.6 ± 1.9 at 8th week to 0.27 ± 0.26 at 54th week ($p=0.0001$). CRP level significantly decreased from week 0 to 54th week ($p<0.0001$). Data are expressed as mean \pm SD.

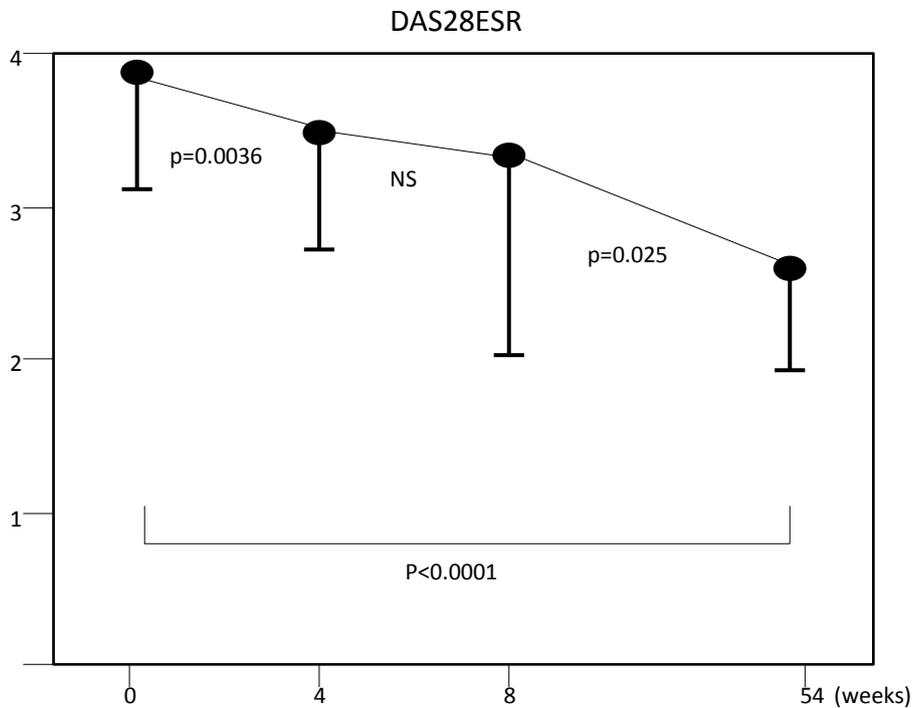


Fig. 3. DAS28ESR levels in the first three visits (0, 4, 8th week), and that at 54th week. DAS28ESR level significantly decreased from 4.0 ± 0.88 to 3.5 ± 0.85 at the 4th week ($p=0.0036$). However, there was no significant difference between DAS28ESR level of the 4th week and that of the 8th week. DAS28ESR level significantly decreased from 3.3 ± 1.2 at 8th week to 2.6 ± 0.67 at 54th week ($p=0.025$). DAS28ESR level significantly decreased from week 0 to 54th week ($p<0.0001$). Data are expressed as mean \pm SD.

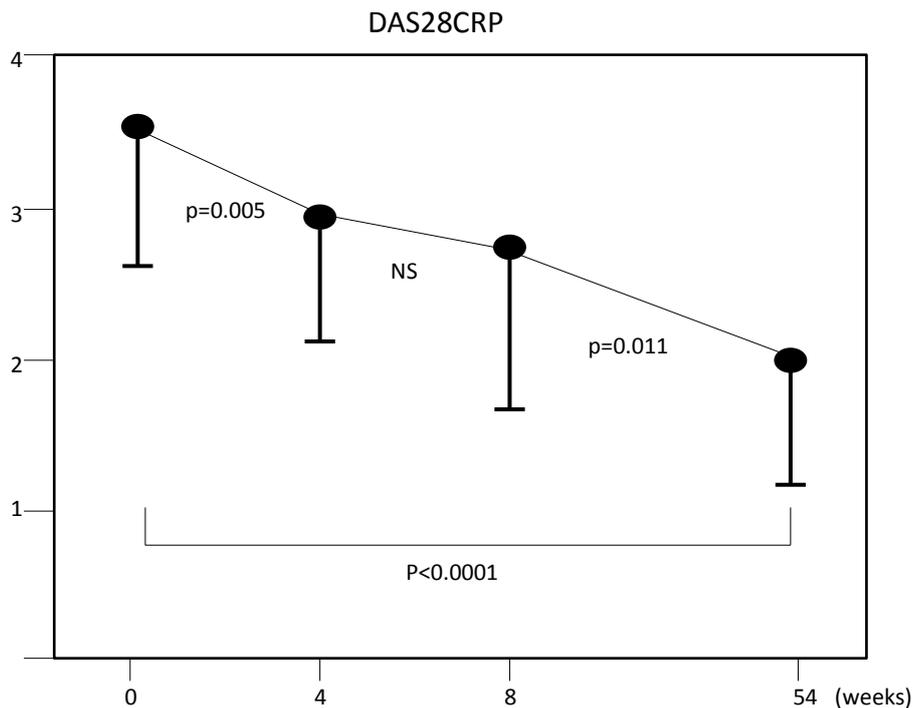


Fig. 4. DAS28CRP levels in the first three visits (0, 4, 8th week), and that at 54th week.

DAS28CRP level significantly decreased from 3.5 ± 0.94 to 2.9 ± 0.89 at the 4th week ($p=0.005$). However, there was no significant difference between DAS28CRP level of the 4th week and that of the 8th week.

DAS28CRP level significantly decreased from 2.8 ± 1.0 at 8th week to 2.0 ± 0.73 at 54th week ($p=0.011$).

DAS28CRP level significantly decreased from week 0 to 54th week ($p < 0.0001$).

Data are expressed as mean \pm SD.

The first three visits (0, 4, 8th week) to the hospital after administration of Tac were chosen as the times in which we determined ESR, CRP levels, DAS28ESR and DAS28CRP levels.

Figure 1 and 2 show ESR and CRP levels in the first three visits to the hospital, respectively. The mean ESR and CRP levels determined in the patients at the initiation of Tac treatment were 37 ± 17 mm/hr and 1.9 ± 1.5 mg/dl, respectively.

ESR and CRP levels significantly decreased from 37 ± 17 to 32 ± 18 and from 1.9 ± 1.5 to 1.4 ± 1.5 , respectively, at the 4th week ($p=0.049$ and $p=0.012$, respectively). However, both did not decrease significantly from the levels of the 4th week to those of the 8th week.

Figure 3 and 4 show the DAS28ESR and DAS28CRP levels in the first three visits, respectively. The mean DAS28ESR and DAS28CRP levels determined in the patients at the initiation of Tac treatment were 4.0 ± 0.88 and 3.5 ± 0.94 , respectively.

DAS28ESR and DAS28CRP levels decreased from 4.0 ± 0.88 to 3.5 ± 0.85 and from 3.5 ± 0.94 to 2.9 ± 0.89 , respectively, at the 4th week ($p=0.0036$ and $p=0.005$, respectively). However, both did not

decrease significantly from the levels of 4th week to those of the 8th week.

Obviously, ESR, CRP level, DAS28ESR and DAS28CRP levels significantly decreased at the 4th week.

The additional administration of Tac was effective as determined on the basis of DAS28ESR level according to EULAR response criteria, in 11 out of 16 RA patients (good,10 ; moderate,1) when combined with infliximab, and in 10 out of 12 RA patients (good,9 ; moderate,1) when combined with etanercept. In other words, the additional administration of Tac showed no effect on 5 out of 16 patients treated with infliximab, and 2 out of 12 patients treated with etanercept.

The observation period was extended up to 54 weeks if the additional administration of Tac was effective, and 25 out of 28 patients were enrolled in this study. Three out of 28 patients changed the biologics. Two out of the three patients changed the biologics because the additional administration of Tac was not effective. One out of the three patients changed the biologics because she wished becoming pregnant.

As shown in Figure 1 and 2, ESR and CRP lev-

els significantly decreased from 8th week to 54th week, respectively. ($p=0.012$ and $p=0.0001$, respectively).

As shown in Figure 3 and 4, DAS28ESR and DAS28CRP levels significantly decreased from 8th week to 54th week, respectively. ($p=0.025$ and $p=0.011$, respectively).

Nine out of 28 patients and 11 out of 25 patients achieved remission using the criteria DAS28ESR <2.6^{7,8)} at 8th week and at 54th week, respectively.

Eleven out of 28 patients and 20 out of 25 patients achieved remission using the criteria DAS28CRP <2.3^{7,8)} at 8th week and at 54th week, respectively.

No serious adverse event was observed in these patients during the observation period.

DISCUSSION

Weekly MTX administration is gold standard in RA therapy. The dose approved in Japan is up to 8 mg/week, which is lower than that used in the US and European countries. However, in our experience, the dose of MTX has to be decreased sometimes to less than 8 mg/week because of complications in patients such as leucopenia, refractory cough and nausea. Moreover, a certain proportion of RA patients are resistant and/or intolerant to MTX.

Biologics exhibit significant anti-inflammatory and anti-rheumatic effects. However, not all RA patients show a good response to biologics⁹⁾.

Interestingly, it has been demonstrated that the Th1 : Th2 ratio in the peripheral blood is raised following infliximab treatment¹⁰⁾. From this point of view, treatment with biologics and/or MTX lacks T-cell-targeted immunosuppression. Tac exerts its immunosuppressive effect primarily by interfering with the activation of T-cells. Tac also suppresses the production of cytokines such as IL-2 and TNF α ^{11,12)}. The usefulness of Tac for RA has been demonstrated in double-blind, placebo-controlled, parallel-group studies and controlled studies compared with other drugs^{13,14)}. Tac up to 3 mg/daily is approved to be used for the patients with RA in Japan.

Efficacy of low-dose Tac added to MTX in patients with RA in Japan was demonstrated in retrospective study¹⁵⁾. Interestingly, 2 patients, in whom the effect of Tac was unsatisfactory in combination with etanercept, were not prescribed MTX.

Additional administration of Tac to the treatment with biologics was significantly effective to

suppress the activity of RA in our study. The effect appeared at 4th week. Therefore, if no improvement is observed 4 weeks after the treatment with the combination of a biologic and Tac, one should consider whether to continue the combination therapy or not.

Presently in Japan, three TNF inhibitors and one interleukin-6 inhibitor are available to physicians. We have options to increase the dose of infliximab and/or shorten the interval of infliximab administration. Moreover, we can switch from one biologic to another. However, these alterations of treatment are sometimes troublesome and are sometimes invalid. The strategy to add Tac is easy to carry out without changing the dose and/or interval of biologic administration. Therefore, if the effect of biologics is unsatisfactory, we should consider the addition of Tac.

Quite recently, increase of MTX dose up to 16 mg/week has been approved in Japan. The difference of addition of Tac and increase of the MTX dose should be compared in terms of its effect.

In order to avoid side effects due to immunosuppression, the dose of Tac was limited to be as low as possible. Side effects such as pneumonia were not observed in the patients enrolled in this study. The occurrence of infection and neoplasm should be carefully examined in the future.

The nuclear factor of activated T-cells (NFAT) is a regulator of osteoclastogenesis and is induced by RANKL¹⁶⁾. Tac inhibits osteoclast formation by targeting the NFAT/calcineurin pathway¹⁷⁾. The effect of prevention of bone destruction by this combination therapy is promising; however, the effect of suppression of the destruction of the joint has not been determined yet. Tac may be a promising candidate to suppress activity of RA refractory to the conventional treatment with biologics.

No conflict of interest exists in this study.

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