The Rate of Decrease in the Disease Activity of Rheumatoid Arthritis during Treatment with Adalimumab Depends on the Dose of Methotrexate

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Abstract

Objective The aim of this study was to analyze the efficacy of adalimumab (ADA) in patients with rheumatoid arthritis treated with or without methotrexate (MTX) and determine impact of the MTX dose.

Methods Pearson’s product-moment correlation coefficient was used to assess the correlations between the improvement in the Disease Activity Score (DAS) 28- erythrocyte sedimentation rate (ESR) score and the MTX dose in patients receiving treatment with MTX at a dose of <8 mg/week, 8 mg/week and >8 mg/week.

Patients ADA therapy was initiated in 68 rheumatoid arthritis patients between July 2008 and June 2013. The mean MTX dose was 9.6 ± 2.6 mg/week, and the patients were followed for 24 weeks.

Results The mean DAS28-ESR scores at baseline and week 24 were 4.6 ± 1.3 and 2.7 ± 1.2 in the 60 patients treated with MTX and 4.5 ± 1.0 and 4.2 ± 1.5 in the eight patients treated without MTX, respectively. Clinical remission was achieved in 48% and 25% of the patients, respectively, by week 24. Moreover, 90.0% of the patients taking MTX continued to receive ADA until week 24, while 50.0% of the patients not taking MTX continued to receive ADA until week 24. Among the 35 patients receiving MTX at a dose of >8 mg/week, the DAS28-ESR scores decreased rapidly from 4.4 ± 1.2 at baseline to 3.2 ± 1.1 at week 4 and further decreased to 2.4 ± 1.0 at week 24. Meanwhile, clinical remission was achieved in 57% of the patients receiving MTX at a dose of >8 mg/week and 36% of those receiving MTX at a dose of ≤8 mg/week. A significant correlation was noted between the improvement in the DAS-ESR score and the MTX dose.

Conclusion In this study population, enhanced clinical efficacy of ADA was achieved in combination with the administration of a sufficient dose of MTX, determined to be >8 mg/week.

Key words: adalimumab, concomitant therapy, methotrexate, rheumatoid arthritis, tumor necrosis factor

Introduction

Adalimumab (ADA; Humira®, AbbVie, North Chicago, USA) is a fully human anti-tumor necrosis factor (TNF) α monoclonal antibody. The treatment efficacy of ADA as a biologic therapy for rheumatoid arthritis (RA) is well demonstrated, and the efficacy of this drug in combination with methotrexate (MTX) was well documented in the PREMIER study (1, 2). In a previously published report of a Japanese population, the concomitant use of MTX and ADA was found to be associated with higher efficacy and treatment retention rates (3). In Western countries, the recommended dose of MTX for patients receiving ADA is 15~20 mg/week.

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Received for publication September 16, 2014; Accepted for publication November 16, 2014

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on average. Meanwhile, the approved dose of MTX combined with ADA in Japan was revised in February 2011 based on the results of an analysis of the safety and efficacy of MTX at doses up to 16 mg/week (4). However, only a limited number of patients have received MTX at 28 mg/week in combination with ADA in Japan. Recently, an all-case survey of ADA in 3,000 Japanese patients with RA was undertaken; however, the relationship between changes in the disease activity after ADA therapy and the dose of MTX has not been clarified (5). Recently, the CONCERTO study demonstrated that higher doses of concomitant MTX tend to be associated with improved outcomes in early RA patients under randomized controlled study conditions (6). In the present analysis, we investigated changes over time in the disease activity among patients receiving MTX at doses of <8 mg/week, 8 mg/week and >8 mg/week in combination with ADA and validated the efficacy of ADA+MTX combination therapy under real-world conditions involving a broader range of RA patients, including both those with a long and short disease duration.

Materials and Methods

Patients and ADA therapy

The participants included 68 patients prescribed the subcutaneous administration of ADA at a dose of 40 mg every other week according to the government approved prescribing information for Humira® in Japan between July 2008 and June 2013. This study was carried out in a single-practice setting at Niigata Rheumatic Center, and the patients were followed for at least 24 weeks until the data cut-off point of December 2013. The subjects included patients who discontinued ADA therapy during the 24-week follow-up period. All participants received ADA therapy according to the Guidelines for Anti-TNF Therapy in Rheumatoid Arthritis proposed by the Japan College of Rheumatology (JCR) (7). The JCR criteria are similar to those of the European League Against Rheumatism (EULAR); therefore, this initiative is relevant for populations in other countries. Concomitant treatment with MTX, disease-modifying antirheumatic drugs (DMARDs) other than MTX and/or steroids was prescribed at the discretion of the attending physician. The doses of the concomitant drugs were adjusted according to standard medical practice for controlling the disease activity.

Clinical efficacy and treatment retention rate

The disease activity was assessed using the 28-joint disease activity score based on the erythrocyte sedimentation rate (DAS28-ESR) and DAS28 based on C-reactive protein (DAS28-CRP) values (8). The severity of the patient’s functional disorder was assessed using the modified health assessment questionnaire (mHAQ) (9). The treatment retention rate during the 24-week period was calculated using a Kaplan-Meier analysis, and missing values were replaced according to the last observation carried forward (LOCF) method (10, 11).

MTX dose

The mean MTX dose in each patient receiving MTX and ADA was calculated using the following formula: mean MTX dose=area under curve of the MTX dose (AUC0-24w)/time (24 weeks) (12). The dose of MTX was adjusted in the patients with RA, many of whom were receiving ADA at a stable dose. The patients were classified into three subgroups according to the mean MTX dose: the MTX <8 mg/week group (n=11; 4.0~7.7 mg/week), MTX 8 mg/week group (n=14; 8.0 mg/week) and MTX >8 mg/week group (n=35; 8.3~16.0 mg/week), unless otherwise noted.

Statistical analysis

The baseline patient characteristics were compared between the patients receiving and not receiving MTX in combination with ADA, and the data are expressed as the mean ± standard deviation or number of patients. Statistical significance was tested using the Kruskal-Wallis test (13) or Pearson’s chi-square test (14). Comparisons of the treatment retention rates were made using the log-rank test (15), and Person’s product-moment correlation was used to examine correlations between the changes in the DAS28-ESR scores during treatment and the dose of MTX. A p value of <0.05 was considered to be significant. A Cochran Armitage trend analysis was used to test the therapy response at week 24. For the Cochran Armitage trend analysis, the patients were classified into four subgroups: mean MTX groups of 0, 6, 8 and 10 mg.

Results

Patient characteristics

The data for 68 patients with RA who received ADA therapy at Niigata Rheumatic Center during the period between July 2008 and June 2013 were analyzed. Table summarizes the demographic and clinical characteristics of the participants at baseline. A comparison of the baseline characteristics of eight patients treated without MTX and 60 patients prescribed MTX while under ADA therapy revealed that the two groups differed significantly in age (p=0.0358), Steinbrocker’s class (p=0.0341) (16), and glucocorticoid medication (p=0.0270) and that the patients who received MTX in combination with ADA tended to be younger than those who did not receive MTX. Bio-naïve patients, i.e., those who had not received biologics prior to ADA therapy, accounted for 78.3% and 62.5% of the patients treated with and without MTX, respectively. The mean duration of illness was 10.3 ± 10.3 years in the overall patients, 9.4 ± 9.4 years in the patients who received MTX and 16.7 ± 14.5 years in the patients who did not receive MTX. The duration of illness tended to be shorter in the patients who received MTX during the study period. Patients with advanced
who received combination treatment with ADA and con-

comitant MTX, the dose of ADA was consistently 40 mg. One ADA monotherapy patient was administered 80 mg every other week.

**Efficacy of treatment with ADA in combination with MTX**

Fig. 1a shows the changes over time in the DAS28-ESR scores at weeks 4, 12 and 24 of ADA therapy. The mean DAS28-ESR scores at baseline and week 4 were 4.6 ± 1.3 and 3.5 ± 1.3 in the patients receiving ADA with MTX, respectively, compared to 4.5 ± 1.0 and 4.5 ± 1.3, respectively, in the patients receiving ADA without MTX. A rapid onset of treatment efficacy was observed in the patients receiving ADA in combination with MTX. The mean DAS28-

ESR score at week 24 was 4.2 ± 1.5 (moderate disease activity) in the patients receiving ADA without MTX and 2.7 ± 1.2 (low disease activity) in the patients receiving ADA with MTX. Overall, the mean DAS28-ESR score decreased from 4.5 ± 1.2 at baseline to 2.9 ± 1.3 at week 24. Considering the mean baseline score to be 100%, the DAS28-ESR scores decreased by 37.0% in the overall patients (from 4.6 ± 1.2 (100%) at baseline to 2.9 ± 1.3 (63.0%) at week 24), 6.7% (from 4.5 ± 1.0 (100%) to 4.2 ± 1.5 (93.3%)) in the patients receiving ADA without MTX and 41.3% (from 4.6 ± 1.3 (100%) to 2.7 ± 1.2 (58.9%)) in the patients receiving ADA with MTX. Fig. 1b shows the percentage of patients who achieved clinical remission, defined as a DAS28-ESR score of <2.6 and DAS28-CRP score of <2.3, at week 24 of ADA therapy. Overall, 46% and 54% of the patients achieved DAS28-ESR and DAS28-CRP remission, respectively, at week 24 of ADA therapy; the corresponding percentages were 25% and 25% in the patients receiving ADA without MTX, and 48% and 58% in the patients receiving ADA with MTX. These findings indicate that the rates of clinical remission were twice as high when ADA was used with MTX than when ADA was used without MTX.

The treatment retention rates from weeks 2 to 24 of ADA therapy were calculated in 68 patients. The overall treatment retention rate at week 24 was 85.3%, and 58 patients continued ADA therapy at week 24 and thereafter (Fig. 1c). Meanwhile, the treatment retention rate was 90.0% in the patients receiving ADA with MTX and 50.0% in the patients receiving ADA without MTX (p=0.0002). Reasons for discontinuing ADA therapy among the patients receiving ADA with MTX included the absence of efficacy in two patients, loss of efficacy in one patient and pneumonia (including *Pneumocystis jirovecii* pneumonia and interstitial pneumonia) in three patients. Reasons for discontinuation among the patients receiving ADA without MTX were the absence of efficacy in two patients, loss of efficacy in one patient and generalized eruption in one patient. The reason for not using MTX was patient refusal in two patients, renal dysfunction in one patient, MTX pneumonia in two patients, MTX intolerance in two patients and renal failure in one patient.
Previous reports have demonstrated that the concomitant use of MTX is essential for maximizing the clinical efficacy of ADA (1, 3, 5). In order to further clarify the relationship between the dose of MTX and the clinical efficacy of ADA therapy, the patients were stratified according to the mean MTX dose into the <8 mg/week group (n=11), 8 mg/week group (n=14) and >8 mg/week group (n=35), and the subgroups were compared. The results of the receiver operating characteristic curve analysis indicated that an optimal mean MTX dose for concomitant use with ADA required to achieve a DAS28 low disease activity of 7.7 mg/week, with a DAS28 remission dose of 8.3 mg/week (data not shown), suggesting that the optimal cutoff for stratification is between 7.7 mg/week and 8.3 mg/week, which supports the rational for stratification at a dose of 8 mg/week as a borderline threshold. A comparison of the patient characteristics at baseline revealed significant differences in age, Steinbrocker’s class, and glucocorticoid medication between the subgroups. A comparison of the changes over time in the disease activity from weeks 4 to 24 revealed that the onset of treatment efficacy occurred earlier in the MTX >8 mg/week group; the mean DAS28-ESR score in this group decreased from 4.4 ± 1.2 at baseline, to 3.2 ± 1.1 at week 4 and 2.4 ± 1.0 at week 24. In contrast, the decrease in the disease activity at week 24 in the other two groups was smaller than that observed in the MTX >8 mg/week group, at 3.3 ± 1.3 and 2.9 ± 1.1 in the MTX <8 mg/week group, respectively. When the relative decrease in the DAS28-ESR score during the 24-week ADA therapy period was calculated based on a mean baseline score of 100%, the DAS28-ESR scores decreased by 34.0% [from 4.7 ± 1.4 (100%) to 3.3 ± 1.3 (66.0%)] in the MTX <8 mg/week group, 38.3% [from 4.4 ± 1.2 (100%) to 2.9 ± 1.1 (61.7%)] in the MTX 8 mg/week group and 45.5% [from 4.4 ± 1.2 (100%) to 2.4 ± 1.0 (54.5%)] in the MTX >8 mg/week group. The severity of the functional disorder expressed according to the mHAQ score improved over time in all groups, although no substantial differences were observed among the three groups. These findings indicate that the patients receiving ADA with MTX at a dose of >8 mg/week experienced more potent treatment effects earlier than those receiving ADA with MTX at a dose of ≤8 mg/week.

The percentage of patients achieving a DAS28-ESR score of <2.6 at week 24 was 36%, 36% and 57% in the MTX <8, 8 and >8 mg/week groups, respectively, compared to 45%, 50% and 66%, respectively, for a DAS28-CRP score of <2.3 at week 24. These finding suggest a relationship between the MTX dose and the clinical remission rate. An analysis of the relationship between the changes in the DAS28-ESR (ΔDAS28-ESR) scores and the MTX dose using Pearson’s product-moment correlation revealed a clear positive correlation between the mean MTX dose and the ΔDAS28-ESR value (p=0.0032) (Fig. 3a). Moreover, a trend analysis revealed that combination treatment with ADA and a higher MTX dose preferably achieved a low disease activity according to the DAS28-ESR score (Fig. 3b). Importantly, no significant adverse events were reported in this study, which differs from that previously reported in an ADA post-marketing study (5), and we found no differences in the rates of adverse events based on the MTX dose.

**Discussion**

An initiative entitled, “Treat to Target” (T2T), launched in 2010 has changed the treatment approach for RA (17). Physicians are now expected to implement tight control of RA...
within clear treatment targets. As a typical example of this approach, the approved dose of MTX for the treatment of RA in Japan was revised in February 2011 to reflect an increase from ≤8 mg/week to ≥16 mg/week (4). The PREMIER study showed that combination therapy with ADA and MTX is more effective than MTX or ADA monotherapy alone (1, 2), and the CONCERTO study demonstrated that combination therapy consisting of ADA and MTX with a higher concomitant dose MTX is more effective than that including a lower concomitant dose of MTX in early RA patients. In the present study, we hypothesized that the real-world treatment efficacy of ADA is greater in a broad range of patients with various disease durations receiving ADA with higher-dose MTX than those receiving ADA with lower-dose MTX and compared the data for the three subgroups of patients receiving MTX at doses of ≤8 mg/week, 8 mg/week and >8 mg/week. Although this study was carried out with the intention of reflecting real-world conditions, we conducted in a single-institute analysis in order to identify a treatment strategy resulting in a similar trend to that observed for treatment with ADA and MTX, particularly with respect to the findings that a higher MTX dose results in better clinical outcomes. Consequently, the analysis demonstrated that clinical remission can be achieved in more patients when ADA is administered in combination with MTX at a mean dose of >8 mg/week (Fig. 2c) and revealed a statistically significant correlation between the MTX dose and an improvement in the DAS28-ESR score (Fig. 3a). The subgroups of patients receiving MTX at doses of 8 mg/week and >8 mg/week exhibited numerically the
same rates of achievement of a DAS28-ESR score of <3.2, at 72% and 74%, respectively (Fig. 3b), and the receiver operating characteristic curve analysis further identified a dose of 7.7 mg/week (data not shown, Fisher’s exact test p=0.00106), suggesting that the optimal MTX dose for achieving the treatment target in combination with ADA in Japanese RA patients is near 8 mg/week. This finding is somewhat interesting, as the optimal concomitant MTX dose shown in the CONCERTO trial was 10 mg/week, although that study did not include an 8 mg/week arm, which suggests that the optimal concomitant MTX dose may be lower than 10 mg/week or that this finding is unique to Japanese RA patients.

In the ARMADA study conducted in 2003, Weinblatt et al. administered ADA at doses of 20, 40 and 80 mg in patients with active RA receiving MTX in order to evaluate the American College of Rheumatology (ACR) response and Disability Index of the HAQ over a 24-week treatment period and demonstrated that the addition of ADA resulted in significant, rapid and sustained improvements in the disease activity over 24 weeks compared with that observed in the group treated with MTX plus a placebo (18). In the present study, we increased the dose of MTX within the approved dose range in the patients receiving ADA and observed significant and rapid improvements in the disease activity in relation to the mean MTX dose. Although our study differs from the above study in terms of the order of treatment with MTX and ADA, these findings suggest that the administration of MTX at sufficiently high doses provides additive effects with respect to the pharmacological actions of ADA, treatment with which is not fully effective without adding MTX. In a study on the relationship between the dose and clinical effect of MTX monotherapy, MTX was found to improve the Ritchie articular index, degree of morning stiffness and ESR and CRP values in relation to the dose of MTX (0, 5, 10 and 20 mg/week) (19). Although the approved dose of MTX has been increased to ≥16 mg/week in Japan, there is currently no evidence regarding the use of MTX at a dose of >8 mg/week. The widespread application of MTX therapy at higher doses is expected to result in an increase in the treatment efficacy of ADA combined with MTX.

Bartelds et al. reported that the serum ADA concentrations are decreased in patients who develop anti-ADA antibodies (AAA) and that the disease activity remains high, with clinical remission being difficult to achieve, in patients with AAA (20). A recent report also found that the incidence of AAA is inversely proportional to the dose of MTX administered concomitantly with ADA (21). This relationship between MTX dose and onset of AAA may not be applicable to patients in Japan, since the results were obtained in Western countries, where MTX is administered at a dose of 10–22.5 mg/week; the body size of Western and Japanese patients differs, and the incidence of AAA during ADA monotherapy is approximately 17% in Western patients versus approximately 44% in Japanese subjects (22). No possible mechanisms explaining why the concomitant use of MTX decreases the immunogenicity of ADA have been proposed to date, and there remains a debate regarding the relationship between the efficacy of ADA and the development of AAA. An ADA assessment report of the Food and Drug Administration (FDA) mentioned that, in RA patients, the mean steady-state trough concentration of ADA is increased by the co-administration of MTX. Moreover, the application of MTX reduces ADA apparent clearance after single and multiple dosing by 29% and 44%, respectively (23). However, it has not been clarified whether the change in clearance is due to the expression of AAA or other mechanisms. Although we did not measure the AAA concentrations in this study, we speculate that the concomitant use of MTX improves the clinical and retention rates of ADA therapy by preventing the formation of AAA.

The results of the HARMONY study (3) demonstrated that the administration of MTX is important for maintaining the treatment efficacy of ADA. In the Gruppo Italiano Studio Early Arthritis (GISEA) registry study conducted in Italy, a logistic model analysis of the treatment retention rate of biologic agents revealed that the use of MTX, among other DMARDs applied concomitantly with biologics, is the most important predictor of the treatment outcome (24). These findings indicate that MTX is an important anchor drug for biological therapy. The present findings also highlight the importance of MTX in biological therapy as an agent for maintaining the treatment efficacy of ADA. Although the present results indicated that the administration of high-dose MTX therapy maximizes the treatment efficacy of ADA, we did not analyze the effects of ADA in the patients who had received biologics prior to the ADA therapy, who accounted for 24% of the participants. Further studies should thus be performed to compare the effects of ADA with MTX in bio-naïve and bio-experienced patients in order to assess the relationship between the treatment efficacy and the MTX dose in these patient populations.

In Japan, the guidelines for anti-TNF treatment (7) and government approved prescribing information for ADA (25) were recently revised, and physicians are now able to prescribe ADA and MTX concomitantly in MTX-naïve and bio-naïve patients in the very early phase of RA (within six months of disease onset). Since patients in the early phase of RA may require high doses of MTX, studies should also be conducted in this patient population.

The findings of the present study demonstrated that the administration of MTX at a dose of >8 mg/week is important for maximizing the treatment efficacy of ADA in patients with RA and that the use of high-dose MTX in combination with ADA may decrease the disease activity, increase the treatment retention rate, alleviate functional disorders and increase the clinical remission rate among RA patients in real-world clinical practice.

Author’s disclosure of potential Conflicts of Interest (COI).
The work was originated from Niigata Rheumatic Center, without any grant support.

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