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A Study on the Selection of DMARDs for the Combination Therapy with Adalimumab

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ABSTRACT

We evaluated whether or not the effect of adalimumab (ADA) in combination with the disease-modifying antirheumatic drugs (DMARDs) other than methotrexate (MTX) is comparable to the ADA+MTX therapy for the treatment of rheumatoid arthritis (RA). A total of 216 patients with active RA at Kohnan Kakogawa Hospital and Kobe University Hospital were enrolled. Clinical and functional outcomes were compared among 4 groups, ADA alone (A group), ADA + MTX (B group), ADA + MTX + other DMARDs (C group), and ADA + other DMARDs (D group), and the retention rates of ADA were evaluated with or without MTX. CRP was significantly decreased from initial measurement at 1 month in all 4 groups, but the continuous efficacy with the statistical significance at all measurement points were observed only in combination with MTX ($P<0.05$), which was reflected by significantly higher retention rates. Similarly, the disease activities were improved, and particularly the remission rates (DAS28-CRP < 2.3) of A, B and C groups (>42.9%) were higher than that of D group (29.4%) at 2 year. An index of patients' basic activities of daily living, M-HAQ score of A, B and C groups was also better than that of D group. While, looking at the mean changes of M-HAQ from the baseline at 2 years, potential effect of other DMARDs on M-HAQ was also suggested. The results show that ADA + MTX therapy is significantly superior than ADA + other DMARDs in ameliorating RA.

INTRODUCTION

Adalimumab (ADA), a fully human immunoglobulin G1 (IgG1) monoclonal antibody with a high specificity for TNFα, was approved in June 2008 as the fourth biologic agent for rheumatoid arthritis (RA) therapy in Japan. Thus, including fifth and sixth approved abatacept (ABT) and golimumab (GOL), we have now more options for the treatment with

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RA, and therefore, RA is becoming a potentially curable disease. Nowadays, except for infliximab, combination therapy with methotrexate (MTX) is not mandatory. Further, convenient subcutaneous injections, every other week, of ADA with a specially designed pre-filled syringe make the self-injection easier for the patients. Importantly, methotorexate (MTX) is not mandatory for ADA therapy.

Studies have shown that anti-TNFα agents are more effective in combination with MTX. The combination therapy of etanercept (ETN) with MTX was highly potent as compared with ETN alone as shown in TEMPO and in COMET studies as well (Klaveskog et al, 2004; Weinblatt et al, 1999; van der Heijde et al, 2006; van der Heijde et al, 2007; Emery et al, 2008; Emery et al, 2010; Kameda et al, 2011). In the PREMIER trial with ADA, it has been shown that combination therapy with ADA and MTX led to better clinical, functional, and radiographic outcomes than that of ADA alone in the patients with early RA (Hoff et al, 2011). Inhibition of radiographic progression has been maintained over 5 years (van der Heijde et al, 2010). For the patients with established RA, the combination with ADA and MTX was also effective and prevented radiographic progression over 10 years and improved M-HAQ in DE019 study (Keystone et al, 2011).

Even 5 biologics treatments are available for in the treatment of RA now in Japan, many patients are also treated empirically with disease modifying anti-rheumatic drugs (DMARDs) and in fact, they are effective in ameliorating the symptoms of RA. Taking into consideration of the long-term period required for the therapy of RA, a possibility of the combination therapy of biologics with the DMARDs other than MTX should also be possible in the real world. With regards to this, however, few reports have been published and whether or not the DMARDs other than MTX are also effective remains unclear. In the present study, therefore, we have studied the effectiveness of various DMARDs as a concomitant drug for ADA. We have divided 216 patients with RA into 4 groups: ADA alone, ADA + MTX, ADA + MTX+ other DMARDs and ADA + other DMARDs, and their clinical features were evaluated.

PATIENTS AND METHODS

A total of 216 out-patients with RA fulfilling the 1987 revised American College of Rheumatology (ACR) criteria (Arnett et al, 1987) at Kohnan Kakogawa Hospital and Kobe University Hospital was enrolled. The study was done from June 2008 to May 2011. The patients remained active despite the treatment with at least one traditional and/or DMARDs and biologics were started to receive the treatment of ADA 40mg subcutaneously every other week.

Among 216 patients, 160 (74.1％) were naïve to biologics treatment, whereas 56 (25.9％) had been treated with other biologics prior to ADA (bio-switched group). Details of the bio-switched group (n=56) were: 20 from Infliximab（IFX）, 24 from ETN, 3 from tocilizumab（TCZ）and 9 from more than 2 biologics (Table I). The 216 patients were

Table I. History of biologics prior to ADA

Biologics prior to ADA	No of patients switched (56／216)
IFX	20
ETN	24
TCZ	3
IFX→ETN	5
ETN→TCZ	2
IFX→TCZ	1
IFX→ETN→TCZ	1

divided into 4 groups: ADA alone (A group) (n=37); ADA + MTX (B group) (n=134);, ADA + MTX + other DMARDs (C group) (n=23); ADA + other DMARDs (D group) (n=22) (Table II). The patients were assigned randomly into the 4 groups except that the patients having interstitial pneumonitis were assigned into either A or D groups in a random basis, in order to avoid drug-induced interstitial pneumonitis. By comparing the baseline demographics in the 4 groups, significant difference was observed in the proportion of patients receiving previous biologics therapy and the mean dose of MTX: the dose of MTX in B group was slightly higher than C group. There were no difference in the other items including gender, age of RA onset, the disease duration, the mean age included, RF positive rate, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), swollen joint count (SJC), tender joint count (TJC), 28-joints disease activity score based on CRP (DAS28-CRP), visual analogue scale of patients' assessment (VAS), morning stiffness time, matrix metalloproteinase-3 (MMP-3), grip strength or modified health assessment questionnaire (M-HAQ) (Table II). ADA was subcutaneously administered 40 mg every other week and no patients had received increased dose of ADA up to 80mg.

Demographic and baseline characteristics were analyzed using the Pearson's chi-square test for gender, RF positive and prior biologics rates, and Mann-Whitney U test for the doses of MTX and Kruskal-Wallis test for the others to detect with or without the difference among the baselines. Kaplan-Meier analysis was used to estimate retention rates during the first 36 months (3 years), and the difference in retention curves was examined by means of a log-rank test. The Wilcoxon signed-rank test was used to detect statistically significant differences in disease activity and functional outcomes between baseline and 24 months (2 years). Figures were shown as observed and LOCF （last observation carry forward）method for patients who withdrew before month 24, and LOCF was employed to evaluate all efficacy parameters. Data were analyzed with STAT View for Windows version 5.0 (SAS Institute Inc., Cary, NC, USA), and P values < 0.05 were considered significant.

Table II. Baseline characteristics of patients

Group	A group (ADA alone)	B group (ADA+MTX)	C group (ADA+MTX +DMARDs)	D group (ADA+他のDMARDs)	P values
Patents number	37	134	23	22	
Gender (female/male)	28/9	115/19	15/8	18/4	0.0801
Age of onset (years)	48.9±13.7	48.2±14.9	50.0±10.0	52.6±17.4	0.6216
Disease duration (years)	10.5±10.2	8.5±7.9	10.3±9.8	9.0±8.9	0.7315
Mean age (years)	59.1±11.2	56.1±13.1	59.8±7.3	61.2±15.1	0.1378
RF positive (%)	85.7	85.4	84.6	86.7	0.9989
Prior use of biologics (%)	43.2	25.4	8.7	18.2	0.0182 *
MTX dose (mg/week)		8.2±2.5	6.6±2.4		0.0120 *
CRP(mg/dl)	2.3±2.2	2.4±2.5	2.2±2.4	3.1±2.8	0.6679
ESR(mm/hr)	74.5±29.8	56.2±33.3	54.8±28.5	69.8±31.2	0.0895
TJC	5.7±6.2	6.0±5.3	5.5±4.5	6.9±5.4	0.6974
SJC	5.8±5.7	7.3±5.0	7.8±4.8	7.1±4.8	0.1889
DAS28/4 CRP	4.3±1.4	4.5±1.2	4.6±1.0	4.7±1.2	0.6134
DAS28/4 ESR	5.6±1.2	5.2±1.3	5.3±1.0	5.6±1.0	0.6526
VAS(mm)	44.9±26.4	45.3±26.9	44.4±25.5	49.4±24.1	0.8749
Morning stiffness (min)	45.3±74.5	122.8±284.8	97.5±115.3	237.9±477.7	0.3083
MMP-3(ng/ml)	257.0±176.0	278.2±231.6	303.7±302.2	290.0±282.5	>0.9999
Grip strength (L+R/2mm/Hg)	125.9±59.2	139.5±58.4	175.6±73.6	123.7±32.6	0.1641
M-HAQ	0.5±0.6	0.5±0.5	0.5±0.5	0.7±0.7	0.2883

*p<0.05

RESULTS

In all 4 groups, CRP and ESR significantly decreased from the baseline at 1 month after the treatment, and this decrease was maintained for 2 years at all measurement points in B and C groups ($p<0.05$)（Figure 1）. With regards to DAS28-CRP consisting of VAS, CRP, SJC and TJC, groups A (ADA alone), B (ADA + MTX) and C (ADA + MTX + other DMARDs) were much better than that of D (ADA + other DMARDs) group (Figure 2). This

Figure 1.

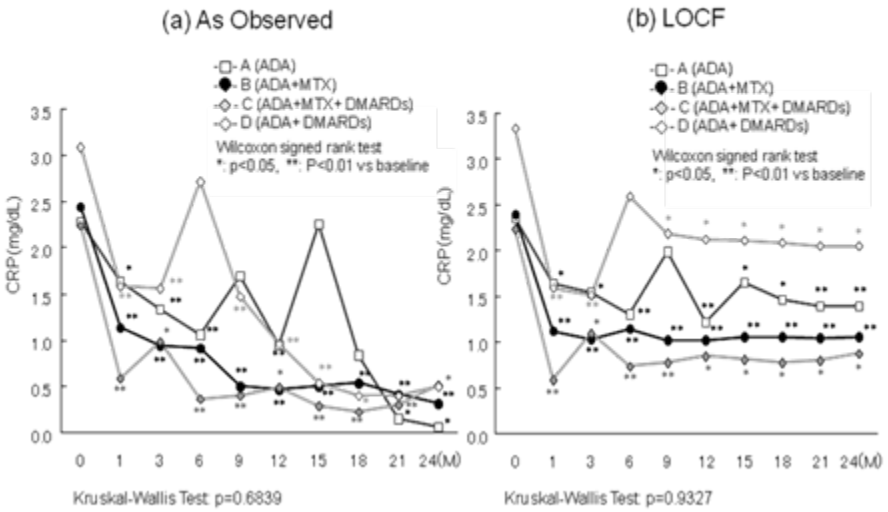


Figure 1. Effect of ADA used alone or in combination with DMARDs on CRP.

Figure 2.

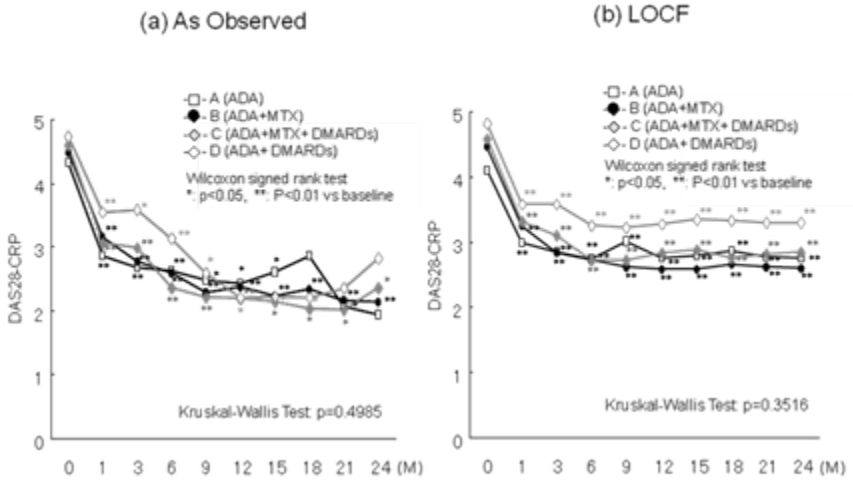


Figure 2. Effect of ADA used alone or in combination with DMARDs on DAS28-CRP.

result was further supported by the percentages of patients who achieved different disease status: high, DAS28-CRP > 4.1; moderate, 2.7 ≤ DAS28-CRP ≤ 4.1; low, 2.3≤ DAS28-CRP < 2.7; and remission, DAS28-CRP < 2.3. The LOCF evaluation showed that the remission rate of D was markedly lower as compared to the A, B and C groups. The values were 42.9%, 47.3%, 42.9% and 29.4% at 24 months after the treatment, respectively (Figure 3).

Figure 3.

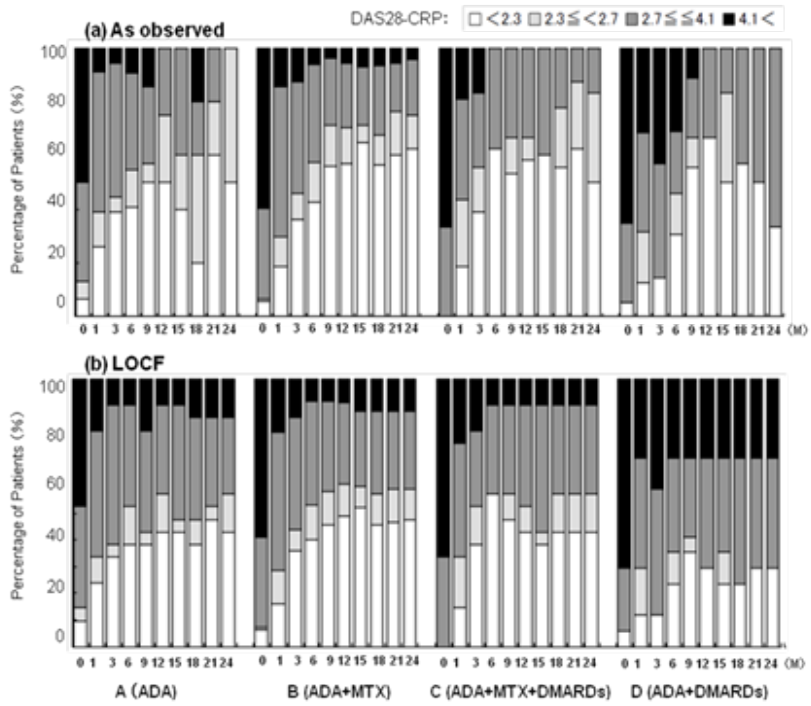


Figure 3. Effect of ADA used alone or in combination with DMARDs on DAS28 disease activity

In addition, M-HAQ scores, an index based on basic activities of daily living (ADL), were also lower in the A, B and C groups as compared with D group, and the functional remission (M-HAQ < 0.5) has been achieved and maintained in the A, B and C groups from 1 month up to 24 months (2 years) after the treatment as shown by LOCF assessment (Figure 4), indicating that the use of MTX in conbination with ADA is more efficacious than the combination with the DMARDs other than MTX.

It was noted, in view of M-HAQ which reflects patients' content to the treatment, that signficant improvements were obtained for the treatment with the DMARDs other than MTX （Figure 5）. When individual DMARDs were examined such as ADA＋MTX, ADA+TAC (tacrolimus), ADA+SASP(salazosulfalyridine), or ADA+BUC (bucillamine), as far as the LOCF analysis shows, DAS28-CRP was highest for ADA when combined with MTX, and the other DMARDs were clealy inferior (Figure 6). The median values at 24 months were 2.3, 3.4, 3.0 and 3.3 in ADA + MTX, ADA+SASP, ADA+SASP, ADA+BUC, respectively, which have shown clinical remission was achieved only in concomitant use of MTX. The superiority of MTX can also be seen in the drug survival, i.e., retention rate of ADA (Figure 7). The retention rate in combination with MTX was significantly higher as compared with

those without MTX ($p < 0.016$): the values were 84.1%, 78.6% and 70.7% at 6 months, 1 year and 2 years, respectively, in patients with MTX. They were 72.9%, 60.5% and 55.8%, respectively, in the patients without MTX.

Figure 4.

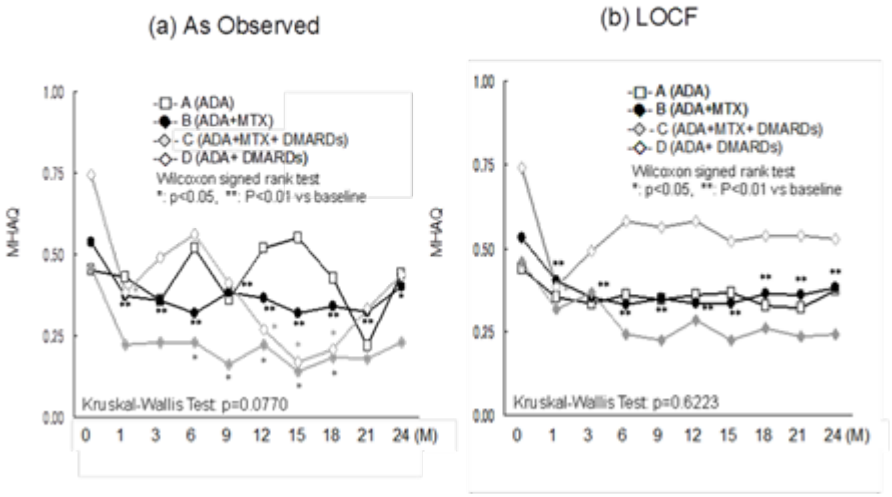


Figure 4. Effect of ADA used alone or in combination with DMARDs on M-HAQ.

Figure 5.

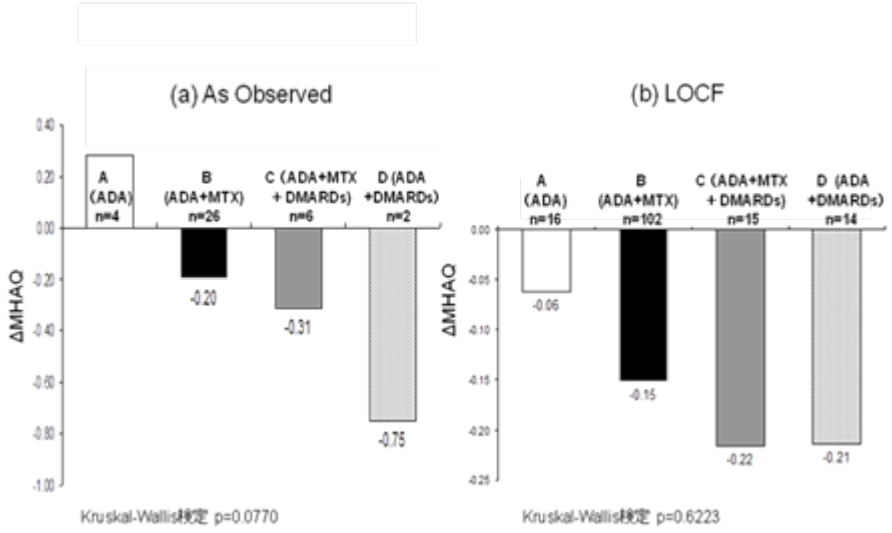


Figure 5. Effect of ADA used alone or in combination with DMARDs on the change of M-HAQ from baseline.

Figure 6.

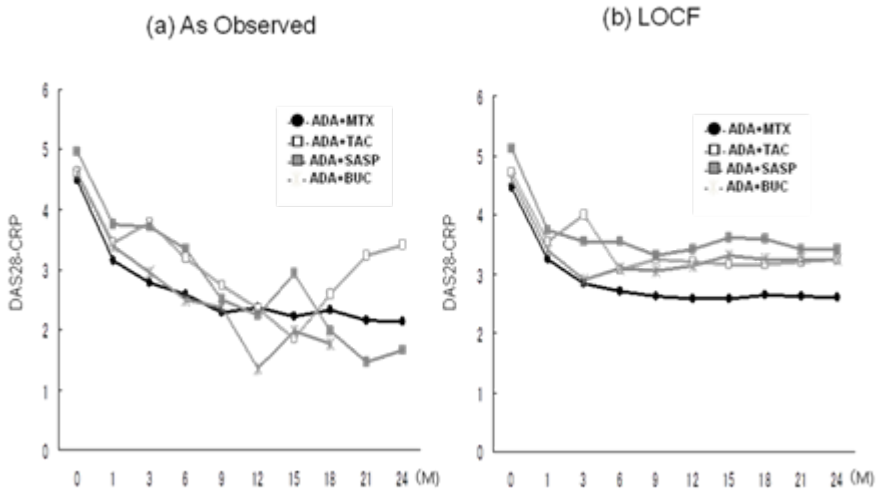
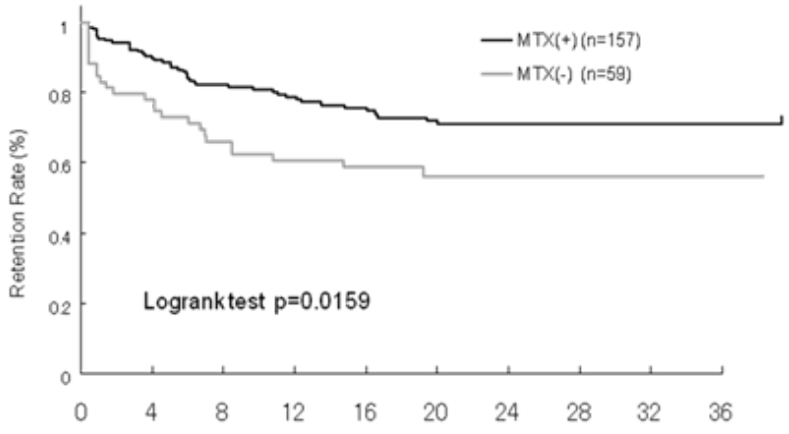


Figure 6. Effect of respective DMARD as added on ADA therapy on DAS28-CRP.

Figure 7.



	6m	12m	18m	24m
MTX(+) (n=157)	84.1%	78.6%	72.8%	70.7%
MTX(-) (n=59)	72.9%	60.5%	58.6%	55.8%

Figure 7. Retension rates of ADA with or without MTX in the ADA therapy.

DISCUSSION

ADA is the fourth approved biologic agent for RA therapy in Japan and therefore predominant patients received other biologics prior to ADA: according to the information of proper use of ADA provided by Abbott Japan (vol.4, interim report with 3084 patients), it has been reported that 50.7% was bio-naïve patients and 49.3% was switched patients from other biologics. In our results, switched cases were also higher in the ADA alone group (A group) (table Ⅰ). Although it is conceivable that more patients with higher disease activity were included in the ADA alone group than other groups, there was no significant difference in the measured items related to joint inflammation such as CRP and ESR, and also the percentages of switched patients between the groups with or without MTX (table Ⅱ), indicating that our evaluation show almost no bias from baseline characteristics. In addition, we showed our results using as observed and LOCF methods. In figures presented at as observed, the efficacy in ADA＋DMARDs group seemed to be similar or somehow better than those of ADA + MTX in some cases. However, the outcomes are coming from the limited patients who have responded to the treatment and no safety issues leading to drop out, and thus we also presented the figures at LOCF, in which missing values are imputed with the last available observation data, so as to consider the outcomes from the patients dropped out due to lack of efficacy and/or safety issues. As the results, the efficacy in ADA+DMARDs group in LOCF was lower than the results in as observed, which indicates that ADA + DMARDs without MTX would brought the higher drop rate than ADA + MTX due to mainly lack of efficacy as supported by the different retention rate between with and without MTX(Figure 7). Thus, because ADA+MTX showed higher improvement rates in DAS28-CRP, clinical and functional remission rates, and drug retention rates as compared to the ADA plus other DMARDs, group (D Group), our results now show that the combination with MTX is superior than those with the DMARDs other than MTX in ameliorating RA.

The efficacy of MTX in combination with biologics is also well established in Japan (Kameda et al, 2011). However, as to the efficacy of the DMARDs other than MTX, there is sole study of Soliman et al (Soliman et al,2011), who compared the retention rates of anti-TNF biologics alone (n=3339) or the combination therapy with MTX (n=4,418), leflunomide (LEF) (n=610), SASP (n=308), MTX + SASP (n=902), MTX + hydroxychloroquine (HCQ) (n=401) or MTX+SASP + HCQ (n=418). The results showed that the highest retention rate was observed in the concomitant use of MTX with biologics. It was reported that LEF and SASP without MTX were not effective, sole exception was the effectiveness of the combination therapy with SASP and ETN. This result was consistent with our results, especially in the drug retention rate. We also newly found that MTX is superior even in ameliorating arthritic signs and symptoms and in particular, MTX was potent in inducing the patients into DAS28-CRP remission.

Noteworthy finding from a clinical point of view would be that the treatment with ADA + other DMARDs (D group) shows best efficacy in MHAQ scoring among the 4 groups (Figure 5). This result is consistent with our clinical experience, that is, DMARDs such as TAC, SASP, BUC are comparably effective in ameliorating joint's symptoms and improve patients' satisfaction in daily clinical practice. However, in face of such clinical improvements, the combination therapy with the DMARDs other than MTX less likely achieves clinical remission to the levels comparalete to ADA plus MTX.

In summary, we have studied the ability of the DMARDs other than MTX as a possible drug of choice in combination with ADA by employing 216 patients with RA. The result shows that ADA leads to higher clinical and functional remission rates in combination with MTX,

but not in combination with other DMARDs. One may also add that other DMARDs are useful in ameliorating the symptoms of RA and improve patients' QOL as reflected by M-HAQ, while not curative.

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