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ORIGINAL ARTICLE

Concomitant methotrexate has little effect on clinical outcomes of abatacept in rheumatoid arthritis: a propensity score matching analysis

Nobunori Takahashi[1] · Toshihisa Kojima[1] · Daihei Kida[2] · Atsushi Kaneko[2] · Yuji Hirano[3] · Takayoshi Fujibayashi[4] · Yuichiro Yabe[5] · Hideki Takagi[6] · Takeshi Oguchi[7] · Masahiro Hanabayashi[8] · Takefumi Kato[9] · Koji Funahashi[10] · Masatoshi Hayashi[11] · Seiji Tsuboi[12] · Yasuhide Kanayama[13] · Yasumori Sobue[1] · Nobuyuki Asai[1] · Takuya Matsumoto[1] · Tatsuo Watanabe[1] · Shuji Asai[1] · Naoki Ishiguro[1]

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Abstract

Objective To compare the clinical outcomes of abatacept between rheumatoid arthritis patients with and without concomitant methotrexate (MTX) treatment in daily clinical practice.

Methods A retrospective cohort study was performed using data from a multicentre registry. A total of 176 consecutive rheumatoid arthritis patients treated with abatacept were included. The propensity score based on multiple baseline characteristic variables was calculated, and 41 of 86 patients treated without MTX (MTX(−)) and 41 of 90 patients treated with concomitant MTX (MTX(+)) were statistically extracted and analysed. Clinical outcomes were evaluated and compared between the two groups over a 52-week period.

Results Baseline characteristics were statistically comparable. No significant differences were observed in the following clinical outcomes from baseline throughout the 52-week period: drug retention rate (MTX(−)/MTX(+) 79.1%/80.5%), mean change in disease activity score based on 28 joints (DAS28-CRP) from baseline (− 1.35/− 1.54), low disease activity rate (48.8%/43.9%), clinical remission rate (31.7%/36.6%), moderate European League Against Rheumatism (EULAR) response rate (68.3%/68.3%), and good EULAR response rate (36.6%/41.1%) at 52 weeks.

Conclusion In rheumatoid arthritis patients with similar background characteristics undergoing abatacept treatment, concomitant MTX does not seem to affect clinical outcomes. Abatacept would be a suitable treatment option in daily clinical practice in patients with contraindications to MTX.

Key Points

- *This is the first study to directly compare the clinical efficacy and safety of abatacept between patients with and without concomitant methotrexate (MTX) treatment in 'real-world' settings using the propensity score matching method.*
- *There were no significant differences in clinical outcomes of abatacept between patients with and without concomitant MTX treatment.*
- *We used data from a large Japanese multicentre registry for biologics in rheumatoid arthritis, thereby decreasing selection bias based on the personal preferences of physicians.*

Keywords Abatacept · Biological DMARDs · Concomitant drug · Methotrexate · Multicentre registry · Propensity score matching · Rheumatoid arthritis

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✉ Nobunori Takahashi
nobunori@med.nagoya-u.ac.jp

Extended author information available on the last page of the article

Introduction

Methotrexate (MTX) has been widely used as the primary drug for rheumatoid arthritis (RA), and its clinical role continues to expand. MTX should be prescribed for most RA patients without a contraindication to MTX, according to the European League Against Rheumatism (EULAR) recommendation [1]

and the American College of Rheumatology (ACR) guideline [2]. If MTX alone does not adequately control the disease, biological disease-modifying antirheumatic drugs (bDMARDs) combined with MTX should be the next step in treatment [1]. However, some patients do not tolerate MTX due to various reasons including renal dysfunction, pulmonary comorbidity, or hepatic dysfunction. In such cases, carefully choosing an optimal class of bDMARDs becomes important.

Three classes of bDMARDs are available now for RA treatment: tumour necrosis factor inhibitors (TNFi), IL-6 pathway inhibitors (e.g. tocilizumab (TCZ)), and abatacept (ABA). ABA inhibits T cell activation by binding to CD80/86, thereby modulating its interaction with CD28. TNFi has been well known to require concomitant MTX treatment for maximal efficacy [3–5]. On the other hand, TCZ does not seem to require concurrent MTX. In the ACT-RAY study, the TCZ monotherapy group demonstrated almost comparable clinical efficacy to the TCZ + MTX group [6]. The 2016 EULAR updated recommendation stated that IL-6 pathway inhibitors may have some advantage compared to other bDMARDs [1].

No randomised controlled trials (RCTs) to date have compared the clinical efficacy of ABA monotherapy and concomitant ABA and MTX treatment in patients with inadequate response to MTX. We have previously reported that concomitant MTX treatment did not improve the short-term clinical efficacy of ABA in daily clinical practice, using the retrospective observational cohort of bDMARDs in Japan, the Tsurumai Biologics Communication Registry (TBCR) [7]. However, retrospective observational studies typically have the limitation of selection bias due to uncontrolled differences between case and control groups. In recent years, propensity score matching analysis has become a popular method to reduce this limitation by adjusting for potential confounding factors [8].

In this study, we compared the clinical efficacy and retention rate during 52 weeks between ABA monotherapy and ABA with concomitant MTX, using data from the Japanese multicentre registry system TBCR. We used propensity score matching analysis to provide new evidence to demonstrate whether MTX improved ABA efficacy among RA patients with similar background characteristics.

Materials and methods

TBCR

The TBCR was developed in 2008 to explore the long-term prognosis of biologics in clinical practice. Registered patients include those who started treatment with biologics at participating institutions [9]. Data in the TBCR are collected prospectively from 2008, as well as retrospectively for patients who had been treated with biologics up until 2008. The number of participating institutions in the TBCR was initially 13, including Nagoya University Hospital, and had increased to a total of 20 in 2015. All 2827 patients registered in the TBCR as of April 2015 met the 1987 ACR criteria or the 2010 ACR/EULAR classification criteria for RA [10]. Information on medication history was collected at clinic visits to TBCR-affiliated institutions. Registry data are updated once per year and include information on whether treatment is being continued, reasons for discontinuation (e.g. insufficient efficacy), and adverse events (AEs). Patient anonymity was maintained during data collection, and security of personal information was strictly controlled. This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine. Written informed consent was obtained from all participants.

Participants

The present study included all patients treated with intravenous ABA and prospectively observed for longer than 52 weeks at TBCR-affiliated institutions ($n = 426$). Patients whose information on baseline variables was available for the estimation of propensity scores were selected ($n = 176$). Since ABA has been commercially available for RA treatment since 2011, data in this study were all prospectively collected. Patients received intravenous ABA infusions three times at 2-week intervals, and thereafter at 4-week intervals, according to drug labels and Japan College of Rheumatology guidelines for treatment. Patients received a fixed dose of ABA at about 10 mg/kg body weight; patients weighing < 60 kg received 500 mg of ABA, those weighing 60–100 kg received 750 mg, and those weighing > 100 kg received 1000 mg.

Data collection

The following data were recorded at the initiation of treatment (baseline, week 0): age, sex, disease duration, serum Krebs von den Lungen-6 (KL-6) level (a specific marker of interstitial pneumonia) [11], estimated glomerular filtration rate (eGFR), joint damage (Steinbrocker stage), daily dysfunction (Steinbrocker class), rheumatoid factor (RF) positivity (≥ 20 IU/ml), history and number of previous bDMARDs, and concomitant treatment (MTX and prednisolone). The following disease parameters were recorded at baseline and after 4, 12, 24, and 52 weeks of treatment: tender joint count (TJC) and swollen joint count (SJC) on 28 joints, patient's (PtGA) and physician's (PhGA) global assessment of disease activity, modified health assessment questionnaire (mHAQ) score [12, 13], serum C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and matrix metalloproteinase-3 (MMP-3) levels. Disease activity was evaluated at each time point using the 28-joint Disease Activity Score with CRP (DAS28-

CRP), which includes data from the above-mentioned disease parameters.

Disease activity and EULAR response

DAS28-CRP is known to significantly underestimate disease activity and overestimate improvement in disease activity compared to DAS28-ESR [14]. In the present study, we used criteria that differed from those of DAS28-ESR. Disease activity was categorised as follows: remission (REM; DAS28-CRP < 2.3), low disease activity (LDA; 2.3 ≤ DAS28-CRP < 2.7), moderate disease activity (MDA; 2.7 ≤ DAS28-CRP ≤ 4.1), and high disease activity (HDA; DAS28-CRP > 4.1). These criteria have been validated in a large Japanese cohort study [15]. Disease activity was evaluated at baseline, 4, 12, 24, and 52 weeks. The EULAR response was evaluated at 4, 12, 24, and 52 weeks [16].

Propensity score matching

In contrast to RCTs, it is difficult to compare efficacy in an observational study because of treatment-selection bias. To overcome this problem, we performed propensity score matching [8]. The propensity score matching method was proposed to statistically evaluate causal effects free from confounding effects, by mathematically refashioning an observational study into a randomised study.

In this study, the propensity score was estimated using a multivariable logistic regression model predicting the use of concomitant MTX using the following key variables: age, sex, disease duration, stature, body weight, prior treatment with biological agents, oral steroid use, DAS28-CRP, TJC, SJC, PtGA, PhGA, ESR, CRP, mHAQ, KL-6, and eGFR. After confirming the sufficient accuracy of this model (the area under the receiver operating characteristic curve was 0.727), we matched 41 patients in each group based on the propensity score. Greedy propensity score matching was implemented (1:1 matching using a calliper of 0.01). In greedy matching, once a match is created, the subject is removed from any further consideration for matching [17].

Statistical analysis

Demographic and disease characteristics were reported using descriptive statistics. All results were expressed as mean ± standard deviation (SD) or percentage (%). Kaplan–Meier curves were generated to estimate the rates of drug continuation and discontinuation due to insufficient efficacy and AEs. Student's *t* test was used for between-group comparisons, and the chi-square test was used for categorical variables. The last observation carried forward (LOCF) method was used in each analysis.

All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$. All analyses were performed with SPSS version 22 software (IBM Corp., Armonk, NY, USA).

Results

Patient baseline characteristics

This study included 90 patients with and 86 patients without concomitant MTX treatment. Propensity score matching was performed, resulting in 41 matched pairs of patients who were treated with concomitant ABA and MTX or with ABA alone. Baseline characteristics of patients are shown in Table 1. There were no significant differences in factors that could affect the decision to prescribe MTX, including age, renal function (eGFR), and serum KL-6 level. There was also no difference in baseline disease activity between the groups.

Comparison of DAS28-CRP scores

Mean DAS28-CRP score significantly decreased from baseline to 52 weeks in both MTX(−) (4.38 ± 1.29 to 3.03 ± 1.40, $p < 0.001$) and MTX(+) (4.63 ± 1.22 to 3.09 ± 1.32, $p < 0.001$) groups (Fig. 1a). Mean DAS28-CRP score significantly decreased from 24 to 52 weeks in the MTX(+) group (3.50 ± 1.42 vs. 3.09 ± 1.32, $p = 0.009$), but not in the MTX(−) group. Mean DAS28-CRP scores and changes in DAS28-CRP scores (Fig. 1b) from baseline were comparable between the two groups, with no significant difference at each time point throughout the 52-week period.

We also examined DAS28-ESR, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) scores as alternative composite measures of RA disease activity. No significant difference was observed between the MTX(−) and MTX(+) groups at each time point (data not shown).

Categorical distribution of DAS28-CRP scores and EULAR response rate

Figure 2a shows the DAS28-CRP categorical distribution of disease activity status. The proportion of patients who achieved LDA or REM significantly increased from baseline to 52 weeks in both MTX(−) (LDA 9.8 to 48.8%, $p < 0.001$; REM 7.3 to 31.7%, $p < 0.001$) and MTX(+) (LDA 2.4 to 43.9%, $p < 0.001$; REM 0.0 to 36.6%, $p < 0.001$) groups. No significant differences were observed in the overall distribution and proportion of patients who achieved LDA or REM at each time point between the two groups throughout the 52-week period.

Table 1 Baseline characteristics of patients

	MTX (−)	MTX (+)	*p* value
n	41	41	
Age (years)	64.7 ± 15.8	63.1 ± 10.1	0.573
Gender (% female)	75.6	90.2	0.078
Disease duration (years)	11.4 ± 11.4	12.2 ± 9.5	0.738
Class (i/ii/iii/iv, %)	12.2/48.8/34.1/4.9	9.8/46.3/41.5/2.4	0.859
RF positive (%)	76.3	84.6	0.358
eGFR	79.1 ± 26.1	77.5 ± 23.0	0.351
KL-6 (U/ml)	297.2 ± 121.1	279.4 ± 156.1	0.566
MTX dose (mg/week)	–	6.9 ± 2.4	–
Oral steroid use (%)	53.7	73.2	0.067
Oral steroid dose (mg/day)[a]	5.1 ± 2.5	4.5 ± 2.8	0.457
TAC use (%)	19.5	12.2	0.364
TAC dose (mg/day)[a]	1.8 ± 0.9	1.6 ± 0.9	0.773
Previous biologics (%)	36.6	53.7	0.120
No. previous biologics[a]	1.3 ± 0.6	1.6 ± 0.7	0.242
DAS28-CRP	4.38 ± 1.29	4.63 ± 1.22	0.365
SJC, 0–28	4.9 ± 5.7	5.0 ± 5.4	0.921
TJC, 0–28	6.6 ± 5.9	8.2 ± 7.1	0.261
CRP (mg/dl)	1.9 ± 3.0	2.3 ± 3.3	0.544
PtGA, 0–100 mm	54.8 ± 29.6	56.4 ± 26.8	0.803
ESR (mm/h)	48.2 ± 33.1	52.7 ± 33.6	0.544
PhGA, 0–100 mm	49.1 ± 23.4	51.0 ± 22.0	0.716
MMP-3 (ng/ml)	241.8 ± 262.5	243.3 ± 348.8	0.983
mHAQ	0.78 ± 0.68	0.90 ± 0.77	0.440

Data are presented as mean ± standard deviation except when otherwise indicated

Class Steinbrocker's classes, *RF* rheumatoid factor, *eGFR* estimated glomerular filtration rate, *KL-6* Krebs von den Lungen-6, *MTX* methotrexate, *TAC* tacrolimus, *DAS28* Disease Activity Score in 28 joints, *SJC* swollen joint count, *TJC* tenderness joint count, *CRP* C-reactive protein, *PtGH* patient's global health assessment, *ESR* erythrocyte sedimentation rate, *PhGH* physician's global health assessment, *MMP-3* matrix metalloproteinase-3, *mHAQ* modified health assessment questionnaire

[a] Mean among patients receiving the drug

The proportions of patients who achieved a moderate or good EULAR response were also evaluated (Fig. 2b). The proportions of patients who achieved a moderate or good EULAR response in the MTX(−) and MTX(+) groups were 41.5% and 58.5% at 4 weeks and 68.3% and 68.3% at 52 weeks, respectively. The proportions of patients who achieved a good EULAR response in the MTX(−) and MTX(+) groups were 14.6% and 14.6% at 4 weeks and 36.6% and 41.5% at 52 weeks, respectively. No significant differences were observed in the overall distribution and proportion of patients who achieved MDA/REM or REM at each time point between the two groups throughout the 52-week period.

Comparisons of clinical and laboratory indices

Next, we examined changes in each component of the DAS28-CRP score (Fig. 3a). In the MTX(−) group, significant decreases from baseline to 52 weeks were observed in TJC (6.6 to 4.3), SJC (4.9 to 2.0), PtGH (54.8 to 29.7), and CRP (1.86 to 0.76). In the MTX(+) group as well, significant decreases from baseline to 52 weeks were observed in TJC (8.2 to 4.2), SJC (5.0 to 1.5), PtGH (56.4 to 33.8), and CRP (2.29 to 0.92). Notably, none of the components showed significant differences between the MTX(−) and MTX(+) groups at each time point during the 52-week period.

We also examined other clinical and laboratory indices for RA activity and functional status (Fig. 3b). In the MTX(−) group, significant decreases from baseline to 52 weeks were observed in PhGH (49.1 to 25.8), ESR (48.2 to 34.9), MMP-3 (241.8 to 136.1), and mHAQ (0.78 to 0.52). In the MTX(+) group, significant decreases from baseline to 52 weeks were observed in PhGH (51.0 to 23.9), ESR (52.7 to 38.0), MMP-3 (243.3 to 126.7), and mHAQ (0.90 to 0.77). Again, no significant differences were observed in these indices between the two groups at each time point during the 52-week period.

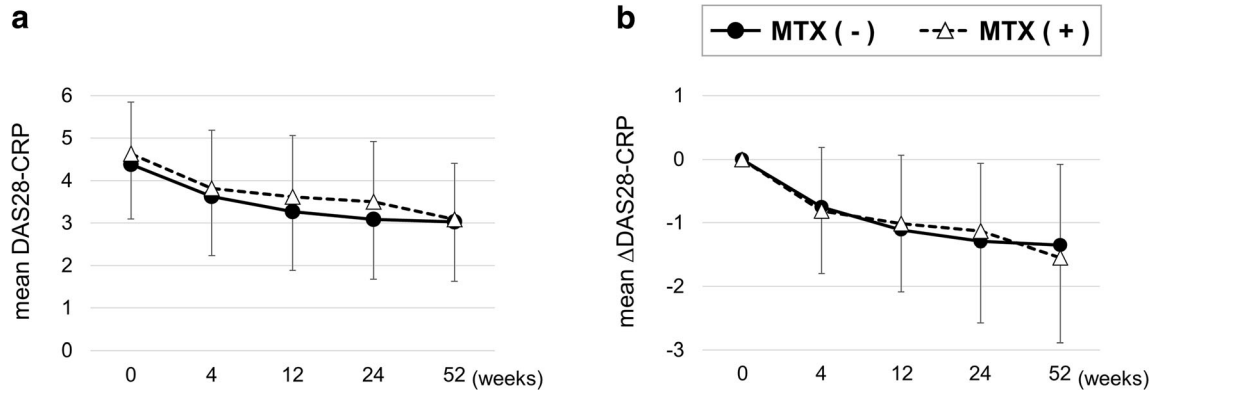

Fig. 1 Comparisons of Disease Activity Score based on 28 joints (DAS28-CRP) between patients with and without concomitant methotrexate (MTX) treatment. **a** Mean and standard deviation (SD) for DAS28-CRP. **b** Change from baseline (triangle) and SD for DAS28-CRP. There was no significant difference between MTX (−) and MTX (+) groups at any time point evaluated by the unpaired *t* test

Comparisons of drug retention rate of ABA

Over 3 years, 10 of 41 patients withdrew from ABA treatment in both the MTX(−) and MTX(+) groups due to inadequate response or AEs. Figure 4a shows the Kaplan–Meier curves displaying the overall drug retention rates in the MTX(−) and MTX(+) groups. Drug retention rates at 3 years were 73.5% in the MTX(−) group and 75.6% in the MTX(+) group, with no significant difference between the two groups ($p = 0.756$ by log-rank test).

The discontinuation rate of ABA due to inadequate response in the MTX(−) group was higher than that in the MTX(+) group, although no significant difference was found (21.7% and 13.4%, respectively, at 3 years; $p = 0.283$). Similarly, the discontinuation rate of ABA due to AEs in the MTX(−) group was lower than that in the MTX(+) group, with no significant difference between the two groups (0.61% and 1.27%, respectively, at 3 years; $p = 0.346$).

Discussion

Concomitant MTX treatment did not affect the clinical efficacy and safety profile within the propensity score matched patients, as we previously reported using unmatched patients in a retrospective study [7]. There were no significant differences between these two groups in mean or change in DAS28-CRP score, categorical distribution of DAS28-CRP scores, EULAR response rate, and discontinuation rate due to inadequate response in the present study. Regarding the safety profile, no significant difference was observed in the discontinuation rate due to AEs between the two groups.

No clinical trial has directly compared ABA monotherapy and ABA with concomitant MTX treatment. The Very Early Rheumatoid arthritis Treatment (AVERT) trial was conducted in early active RA patients who were MTX naive or received MTX (10 mg/week) for 4 weeks with no MTX for 1 month prior to enrolment [18]. Although that study had three arms, i.e. ABA plus MTX, ABA monotherapy, and MTX, the

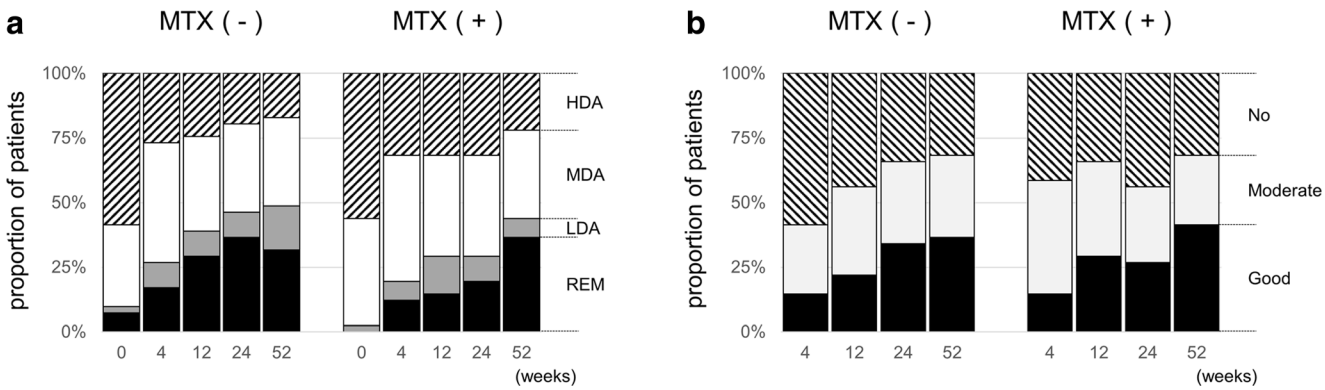

Fig. 2 Comparisons of disease activity and treatment response of patients treated with and without concomitant methotrexate (MTX). **a** Disease Activity Score based on 28 joints (DAS28-CRP) in patients with and without concomitant MTX treatment. Disease activity was categorised as follows: remission (REM; DAS28-CRP < 2.3), low disease activity (LDA; 2.3 ≤ DAS28-CRP < 2.7), moderate disease activity (MDA; 2.7 ≤ DAS28-CRP ≤ 4.1), and high disease activity (HDA; DAS28-CRP > 4.1). **b** European League Against Rheumatism (EULAR) response based on DAS28-CRP in patients with and without concomitant MTX treatment

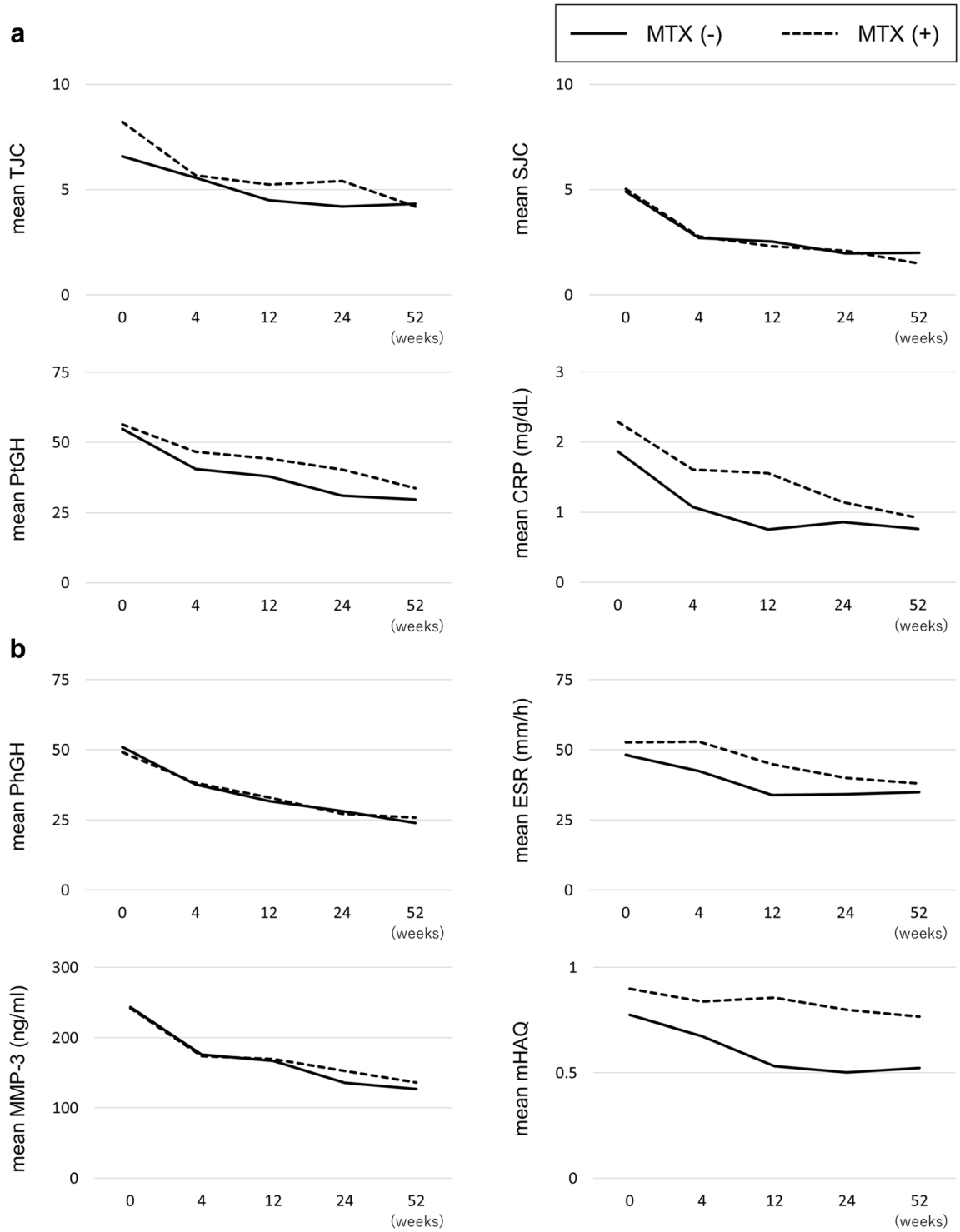

Fig. 3 Comparisons of disease activity indices and physical function between patients with and without concomitant methotrexate (MTX) treatment. **a** Disease Activity Score based on 28 joints (DAS28-CRP); tenderness joint counts (TJC), swollen joint counts (SJC), patient's global health assessment (PtGH), and C-reactive protein (CRP). **b** Other disease activity indices and physical function; physician's global health assessment (PhGH), erythrocyte sedimentation rate (ESR), matrix metalloproteinase-3 (MMP-3), and modified health assessment questionnaire (mHAQ)

primary end point was DAS28-CRP < 2.6 for ABA plus MTX versus MTX. The proportions of patients who achieved the primary endpoint were 61.3% in ABA plus MTX, 43.1% in ABA monotherapy, and 45.7% in the MTX arm. Although the difference between ABA plus MTX and ABA monotherapy arms was not statistically evaluated, concomitant MTX

apparently increased the clinical efficacy among early active RA patients who were MTX naive. Thus, specific patient groups appear to benefit from concomitant MTX to maximise ABA efficacy. However, the very uniform background characteristics of the patients in the AVERT trial were quite different from those of diverse patients in daily clinical practice. Therefore, clinical data obtained from the 'real-world' registry data would be more generalisable to patients in daily practice.

The results of the AVERT trial prompted us to revisit our previous conclusion that concomitant MTX treatment does not improve the short-term clinical efficacy of ABA in daily clinical practice [7]. To this end, we re-compared DAS28 scores between patients treated with and without concomitant MTX among all patients treated with ABA. The analysis revealed that DAS28 scores were significantly lower in the MTX (+) group compared to those in the MTX (−) group (Fig. S1). However, there were several significant differences in baseline variables between groups (Table S1), which led us to conduct the present propensity score matching analysis.

In principle, we use MTX in all patients without contraindications. Based on the data from the present study, however, MTX may be dispensable for patients undergoing ABA treatment. Patients with high disease activity are less likely to achieve good clinical results (LDA or clinical remission) with ABA treatment [19]. These patients should undergo sufficient MTX treatment first to maximally suppress disease activity before starting ABA to optimise the clinical response. However, for patients with a contraindication to MTX, ABA may be a suitable treatment option since the two medications have little additive or synergistic clinical effect.

We also reported on the beneficial effect of concomitant tacrolimus on the efficacy of ABA in a previous study [20, 21]. The differences in percent use and dose of tacrolimus were no longer significant after propensity matching in the present study.

Baseline disease activity was relatively moderate in the present study. We previously reported that tocilizumab, an IL-6R inhibitor, demonstrated a stronger clinical response with concomitant MTX in patients with high disease activity [22], despite other reports suggesting that tocilizumab does not require concomitant MTX [6, 23]. In the case of ABA, concomitant MTX might be necessary when treating patients with high disease activity. Further studies will be needed to address this clinically relevant issue.

The mean age of patients in the present study was slightly higher than that reported in a Japanese PMS study [24]. Nonetheless, propensity score matching can only be used to compare patients with matched background characteristics. In this regard, comparisons based on particular characteristics, such as disease activity and age, could be informative.

A major limitation of this study is the small sample size. Although the statistical power of our analysis was insufficient to reach a firm conclusion, the difference between groups with and without MTX treatment was also apparent in our previous study on adalimumab. That study included 33 patients treated with MTX and 16 patients treated without MTX [4] and found that combination therapy of adalimumab with MTX was significantly more effective compared to adalimumab alone. In the present case, we believe that MTX is less important for maximizing the initial efficacy of ABA treatment in contrast to the case of TNF inhibitors. This study has additional limitations. First, we have no data on the concomitant use of conventional synthetic DMARDs other than MTX, which could have affected the clinical efficacy of ABA. Second, our findings would need to be re-examined in the future if a new confounding factor is discovered, since the propensity score matching method cannot control for unknown confounding factors. Third, sequential radiographic data were not available. Given the importance of joint protective effects in demonstrating clinical efficacy, evaluating radiographic changes in patients treated with ABA will be necessary in the future. Finally, the present study findings were all based on the use of intravenous ABA. The use of a new subcutaneous formulation is now widespread; thus, further investigation is needed to determine whether our results apply to subcutaneous ABA as well.

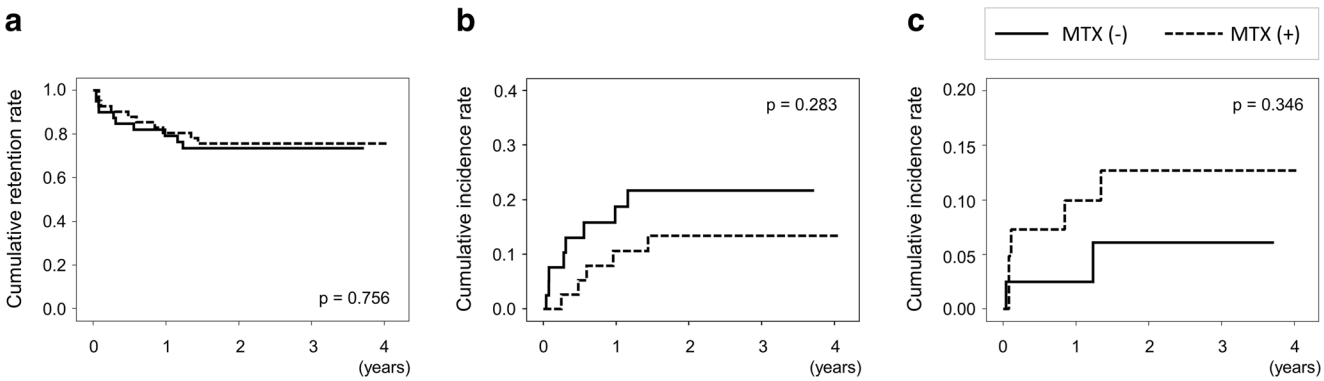

Fig. 4 Comparisons of Kaplan–Meier curves for time to discontinuation of abatacept for patients with and without concomitant methotrexate (MTX) treatment. **a** Overall drug retention rate. **b** Drug discontinuation rate due to inadequate response. **c** Drug discontinuation rate due to adverse events

Conclusion

In RA patients with similar background characteristics, concomitant MTX treatment does not seem to affect the clinical efficacy and safety of ABA. ABA would be a suitable treatment option for patients with contraindication to MTX in daily clinical practice.

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Compliance with ethical standards This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine. Written informed consent was obtained from all participants.

Conflict of interest N.I. received grants, lecture fees, and fees for serving on speakers' bureaus from Daiichi Sankyo, Takeda Pharmaceutical, Hisamitsu Pharmaceutical, Otsuka Pharmaceutical, Taisho Toyama Pharmaceutical, Kaken Pharmaceutical, Eisai, Janssen Pharmaceutical, Bristol-Myers Squibb, Abbott Japan, Chugai Pharmaceutical, Mitsubishi Tanabe Pharmaceutical, Astellas Pharma, and Pfizer Japan. T.K. received lecture fees (< US$5000) from Mitsubishi Tanabe Pharma, Takeda Pharma, Eisai Pharma, AbbVie, Bristol-Myers Squibb, and Pfizer and $10,000 from Chugai Pharma. N.T. received speaker's fees from Abbott Japan, Eisai, Mitsubishi Tanabe Pharma, Pfizer, Chugai Pharmaceutical, and Bristol-Myers Squibb (< $5000). Y.H. received speaker's fees from Abbott Japan, Eisai, Mitsubishi Tanabe Pharma, Pfizer, Chugai Pharmaceutical, and Bristol-Myers Squibb (< $5000). A.K. received lecture fees (< $5000) from Mitsubishi Tanabe Pharma, Takeda Pharma, Eisai Pharma, Chugai Pharma, Abbott, Bristol-Myers Squibb, UCB, Janssen, and Pfizer. All other authors have no conflict of interest to report.

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Affiliations

Nobunori Takahashi[1] · Toshihisa Kojima[1] · Daihei Kida[2] · Atsushi Kaneko[2] · Yuji Hirano[3] · Takayoshi Fujibayashi[4] · Yuichiro Yabe[5] · Hideki Takagi[6] · Takeshi Oguchi[7] · Masahiro Hanabayashi[8] · Takefumi Kato[9] · Koji Funahashi[10] · Masatoshi Hayashi[11] · Seiji Tsuboi[12] · Yasuhide Kanayama[13] · Yasumori Sobue[1] · Nobuyuki Asai[1] · Takuya Matsumoto[1] · Tatsuo Watanabe[1] · Shuji Asai[1] · Naoki Ishiguro[1]

1 Department of Orthopedic Surgery and Rheumatology, Nagoya University Hospital, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan

2 Department of Orthopedic Surgery and Rheumatology, Nagoya Medical Center, 4-1-1 Sanno-maru, Naka-ku, Nagoya, Aichi, Japan

3 Department of Rheumatology, Toyohashi Municipal Hospital, 50 Hakken-nishi, Aotake-cho, Toyohashi, Aichi, Japan

4 Department of Orthopedic Surgery, Konan Kosei Hospital, 137 Oomatsubara, Takaya-cho, Konan, Aichi, Japan

5 Department of Rheumatology, Tokyo Shinjuku Medical Center, 5-1 Tsukudo-cho, Shinjuku-ku, Tokyo, Japan

6 Department of Orthopedic Surgery, Nagoya Central Hospital, 3-7-7 Taiko, Nakamura-ku, Nagoya, Aichi, Japan

7 Department of Orthopedic Surgery, Anjo Kosei Hospital, 28 Higashihirokute, Anjo, Aichi, Japan

8 Department of Orthopedic Surgery, Ichinomiya Municipal Hospital, 2-2-22 Bunkyo, Ichinomiya, Aichi, Japan

9 Kato Orthopedic Clinic, 8-4 Minami-myoudaiji-cho, Okazaki, Aichi, Japan

10 Department of Orthopedic Surgery, Kariya–Toyota General Hospital, 5-15 Sumiyoshi-cho, Kariya, Aichi, Japan

11 Department of Rheumatology, Nagano Red Cross Hospital, 5-22-1 Wakazato, Nagano, Japan

12 Department of Orthopedic Surgery, Shizuoka Kosei Hospital, 23 Kitaban-cho, Aoi-ku, Shizuoka, Japan

13 Department of Orthopedic Surgery, Toyota Kosei Hospital, 500-1 Ibohara Josui-cho, Toyota, Aichi, Japan