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ORIGINAL ARTICLE

Predictive value of baseline concomitant glucocorticoid for abatacept-mediated long-term inhibition of radiographic progression: insights from the KURAMA cohort

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ABSTRACT

Abatacept (ABT) is a biological disease-modifying antirheumatic drug (bDMARDs) for rheumatoid arthritis (RA) when conventional synthetic DMARDs are ineffective. We aimed to evaluate the long-term effects of ABT on joint destruction in patients treated for over 2 years. Radiographic progression was evaluated using the van der Heijde-modified Total Sharp Score (mTSS) by two rheumatologists at ABT initiation and after 2 years. Multivariate logistic regression analysis was used to identify factors associated with structural remission, defined as the mean annual change in mTSS $\leq$0.5. Among the 111 patients included, 48 discontinued, and 63 continued ABT treatment until radiographic evaluation was performed. The rate of patients who achieved estimated TSS REM (yearly progression of van der Heijde modified total Sharp scores $\leq$0.5) was significantly lower in ABT-dropouts than in the ABT-continued group (69% vs. 48%, $p = .0336$ by Fisher's exact test). Among the continued ABT cases, concomitant glucocorticoid treatment at ABT initiation was the strongest negative predictive factor of estimated TSS REM in univariate and multivariate logistic regression analyses. Radiographic progression after ABT administration should be evaluated separately for dropout and non-dropout cases. Glucocorticoids at the initiation of ABT may serve as a predictive factor for joint destruction in long-term ABT use.

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KEYWORDS
Abatacept; modified total sharp score; radiographic progression; rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is characterized by gradual joint deterioration, which leads to a substantial decline in physical function and quality of life (QOL). Synovial inflammation and osteoclast activation are crucial in the pathogenesis of rheumatoid arthritis. These conditions lead to the destruction of bone and cartilage, significantly impairing joint function [1].

Treatment guidelines across various countries recommend adding or switching to biological or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs or tsDMARDs) when the therapeutic effect of methotrexate is insufficient [2]. Abatacept (ABT) is a bDMARD composed of the extracellular domain of human cytotoxic T lymphocyte-associated molecule-4 (CTLA-4) fused to the Fc portion of human immunoglobulin G. ABT specifically binds to the cluster of differentiation (CD)80/86 on antigen-presenting cells (APCs), leading to the inactivation of T cells. Unlike other bDMARDs that target inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) or interleukin 6 (IL-6), ABT possesses a distinct mechanism of action. Clinical trials have demonstrated that ABT exhibits comparable radiographic outcomes to other agents, indicating its therapeutic effectiveness [3,4]. However, few studies have examined the protective effects of ABT against joint destruction after

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long-term use. Furthermore, the predictive factors for such effects are unknown.

In this study, our assessment focused on measuring joint damage using the van der Heijde-modified Total Sharp Score (mTSS) in patients who had received ABT for > 2 years. Additionally, our objective was to identify the factors that could predict ABT's long-term effectiveness of ABT in inhibiting radiographic progression.

2. Materials and methods

2.1. Study design and patient selection

All patients who fulfilled the 1987 and/or 2010 classification criteria for RA [5,6] at Kyoto University Hospital were registered in a prospective study named the KURAMA cohort. As previously described [7,8], clinical data were recorded at baseline and every visit in the database. The present study was conducted retrospectively using the database. We included patients who visited Kyoto University Hospital between May 2011 and April 2021 and received ABT treatment intravenously or subcutaneously and whose X-ray assessment was feasible from the initiation of ABT to more than two years.

2.2. Clinical characteristics

The medical records of the patients were retrospectively reviewed, including age, sex, disease duration, medication, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) level, swollen joint count, tender joint count, physician's global assessment of RA activity, patient's global assessment of RA activity, and the titers of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPAs). RF and ACPA were considered positive if the titers were > 15 IU/mL or RF and more than 4.5 U/mL for ACPA. The clinical disease activity index (CDAI) was used to monitor the disease activity. CDAI score was monitored as observed, that is, irreverent with continuous use of ABT or not.

2.3. Evaluation of joint destruction by mTSS

Radiographs of each patient's hands and feet were taken at the time of ABT initiation and at least 2 years after induction; if multiple radiographs were taken after 2 years, the final radiograph was examined. Radiographic progression was evaluated by two rheumatologists (RW and KM) who were trained and certified by Prof. van der Heijde (Leiden University) using the mTSS scoring system [9–11]. The CAC Corporation provided a dedicated DICOM viewer. The progression of the mTSS per year (delta TSS/year) was calculated from the mean progression by the two readers and the duration of ABT administration. If ΔmTSS/year differed by 10 or more, the two rheumatologists discussed it and reached a shared conclusion. Structural remission was defined as delta TSS/year $\leq$0.5 [12], and clinically relevant radiographic progression (CRRP) was defined as ΔmTSS/year >3 [13].

2.4. Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki, the study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (No. R0357), and written informed consent was obtained from all patients.

2.5. Statistical analyses

All statistical analyses were performed using the JMP Pro 16.2.0 (SAS Institute). The Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables were used. A multivariate logistic regression model was used to evaluate the factors associated with long-term structural remission. *p*-Values of less than .05 were considered statistically significant.

3. Results

3.1. Clinical characteristics of patients at the initiation of ABT

One-hundred-eleven patients who initiated ABT therapy and were available for radiography for > 2 years were included in this study. The interobserver reliability of delta TSS as determined by intraclass correlation coefficients (ICC [1,2]) was 0.912, and only 11 patients required a re-evaluation of radiographs. The smallest detectable change of delta TSS/year in the present study was calculated as 0.837, defined in the previous report by the following formula [14]. Among them, 63 patients continued ABT (including one patient who had stopped 9 months later because of clinical remission with no recurrence until follow-up X-ray examination), and 48 patients discontinued ABT for any unfavorable reason (among them, 62.5% by insufficiency, 25.0% by adverse events). As shown in Table 1, compared to those who dropped out, patients who continued ABT were older (59.5 vs 67 years) and tended to show lower CDAI after 12 months. The occurrence of concomitant interstitial lung disease (ILD) was similar between the two groups. Unfortunately, we were unable to determine the precise rate of osteoporosis complications as not all patients underwent

Table 1. Comparison between patients who dropped out or continued ABT until radiographic progression over than 2 years was evaluated.

	ABT-dropped out	ABT-continued	*p*-Value
Patients (*n*)	48	63	
Age (year, median, IQR)	59.5 (51.3–67.5)	67 (58–73)	.0064
Female (*n*, %)	29 (81%)	52 (83%)	1.0000
Disease duration (year, median, IQR)	7 (3–12)	7.5 (3–17.5)	.5294
RF-positive (*n*, %)	39 (81%)	51 (81%)	1.0000
ACPA-positive (*n*, %)	41 (85%)	57 (90%)	.5531
Lung involvement	25 (52%)	31 (49%)	.8487
Duration of ABT administration (month, median, IQR)	7.5 (1.5–14)	66 (49–83)	<.0001
Concomitant MTX at ABT introduction (*n*, %)	31 (65%)	40 (63%)	1.0000
MTX dose (mg/w, median, IQR)	6 (0–8)	4 (0–8)	.7449
Concomitant GC (*n*, %)			
Baseline	23 (48%)	31 (51%)	.8487
At the time of follow-up X-ray	27 (43%)	20 (42%)	1.0000
GC dose (mg/d as PSL equivalent, median, IQR)			
Baseline	0 (0–5.375)	1 (0–5)	.9720
At the time of follow-up X-ray	0 (0–5)	0 (0–4)	.7502
Concomitant denosumab (*n*, %)	9 (14%)	4 (8%)	.8365
Concomitant bisphosphonate (*n*, %)	20 (42%)	20 (32%)	.3216
History of b/tsDMARDs (*n*, %)	25 (52%)	23 (37%)	.1223
ESR (mm/h, median, IQR)	31 (12–67)	32.5 (20.8–60)	.8010
CRP (mg/dL, median, IQR)	0.4 (0.1–2.4)	0.7 (0.2–2.2)	.1954
CDAI at ABT introduction (median, IQR)	14.7 (4.95–22.0)	13.7 (9.2–22.7)	.4921
CDAI at 1 months (median, IQR)	10.3 (4.2–16.7)	8.7 (5.6–12.8)	.7321
CDAI at 3 months (median, IQR)	6.7 (3.6–14.0)	7.8 (4.5–11.43)	.8040
CDAI at 6 months (median, IQR)	7.6 (2.4–14.8)	6.1 (2.4–9.4)	.1858
CDAI at 12 months (median, IQR)	6.9 (4.4–12.8)	5.1 (2.5–8.4)	.0244
CDAI at 24 months (median, IQR)	7.2 (2.2–14.9)	4.4 (1.9–7.0)	.0015
CDAI at 36 months (median, IQR)	6.0 (2.8–12.8)	4.8 (1.5–8.3)	.0358
Any targeted DMARDs (after dropping out of ABT)	34 (71%)	–	N.A
Anti-TNF	20 (42%)	–	N.A
Anti-IL6 receptor	17 (35%)	–	N.A
Abatacept (rechallenge)	2 (4%)	–	N.A
JAK inhibitor	6 (13%)	–	N.A
Baseline TSS (median, IQR)	50.5 (15.1–97.3)	42 (13–112)	.8911
Steinblocker's roentgenograms stage	I: 19, II: 20, III: 9, IV: 0	I: 33, II: 20, III: 9, IV: 1	.4269
Interval of delta TSS assessment (month, median, IQR)	37.2 (35.2–41.2)	37.4 (35.6–39.9)	.9881
Delta TSS (median, IQR)	0 (0–3.8)	2 (0–6)	.0810
Delta TSS/year (median, IQR)	0 (0–0.94)	0.56 (0–2.0)	.0900
Delta TSS/year < 0.5 (*n*, %)	33 (69%)	30 (48%)	.0336

p-Values were calculated to compare the clinical characteristics of patients between patients who dropped out ABT and who continued ABT at the time of follow-up X ray. Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables. ABT: Abatacept, IQR: interquartile range; RF: Rheumatoid factor; ACPA: anti-cyclic citrullinated peptide antibodies; MTX: Methotrexate; GC: Glucocorticoid; b/tsDMARDs: biological or targeted synthetic DMARDs; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CDAI: clinical disease activity index, TNF: tumor necrosis factor, IL-6: interleukin-6, JAK: janus kinase, TSS: Total Sharp Score, N.A: not analysed.

dual-energy X-ray absorptiometry. However, it's noteworthy that denosumab and bisphosphonate usage was comparable between the groups. Unexpectedly, the percentage of the patients who achieved radiographic remission (estimated TSS REM), defined as delta TSS/year < 0.5, was significantly higher in dropped-out cases than in ABT-continued cases (69% vs 48%, $p = .0336$). Following the discontinuation of ABT, targeted DMARDs were introduced in 34 patients, constituting 71% of the ABT-dropped out cases.

3.2. Structural remission rate by long-term administration of ABT

The patients were divided into those who achieved estimated TSS REM and those who did not, and the clinical profiles were compared to reveal the factors that predict structural remission among patients who continued ABT for > 2 years (Table 2). Those who achieved structural remission had a relatively lower rate of glucocorticoid use than those who did not (33% vs. 67%, $p = .0118$, Figure 1(A)). A lower TSS at the baseline period was also a significant prediction factor (26.5 vs 52, $p = .0376$). By putting a ROC curve (receiver operating characteristic curve) to perform classification thresholds of the best cut-off point to predict estimated TSS REM, 14 baseline TSS were defined, which was also revealed as a significant prediction factor (TSS REM rate was 85% in those who under 14 baseline TSS vs. 60% in those who over 14, $p = .0452$, Figure 1(B)). However, all other components were comparable between the patients who achieved the estimated TSS REM and the others, including ACPA positivity and disease activity throughout the observation period. The proportion of concomitant GC usage and the dosage of GCs at the final X-ray evaluation timepoint were similar between the group that achieved TSS REM and the group that did not. Furthermore, the TSS REM rates were comparable between the GC-withdrawn cases ($n = 8$, 33%) and the cases where GC usage continued ($n = 2$, 25%).

Table 2. Comparison between patients who achieved estimated TSS REM or not.

	Estimated TSS REM not achieved	Estimated TSS REM achieved	*p*-Value
Patients (*n*)	33	30	
Age (year, median, IQR)	67 (58–74)	67 (59–72)	.8255
Female (*n*, %)	29 (88%)	23 (77%)	.3247
Disease duration (year, median, IQR)	7 (3–13)	8 (2–14)	.9291
RF-positive (*n*, %)	27 (82%)	24 (80%)	1.0000
RF value (IU/mL)	43.7 (17.4–110.2)	43.4 (17.2–101.1)	.8905
ACPA-positive (*n*, %)	30 (91%)	27 (90%)	1.0000
ACPA value (U/mL)	83.9 (22.2–194)	87.5 (35.2–201.5)	.6447
Lung involvement	15 (45%)	16 (53%)	.6173
Concomitant MTX at ABT introduction (*n*, %)	19 (58%)	21 (70%)	.4325
MTX dose (mg/w, median, IQR)	4 (0–8)	5 (0–8)	.3984
Concomitant GC (*n*, %)			
Baseline	22 (67%)	10 (33%)	.0118
At the time of follow-up X-ray	17 (51%)	10 (33%)	.2034
GC dose (mg/d as PSL equivalent, median, IQR)			
Baseline	4 (0–5)	0 (0–2.8)	.0137
At the time of follow-up X-ray	0 (1–5)	0 (0–2)	.0814
Concomitant denosumab (*n*, %)	5 (15%)	4 (13%)	1.0000
Concomitant bisphosphonate (*n*, %)	14 (42%)	6 (20%)	.0649
History of b/tsDMARDs (*n*, %)	13 (39%)	10 (33%)	.7938
ESR (mm/h, median, IQR)	29 (23–60)	36 (20–55)	.8689
CRP (mg/dL, median, IQR)	1.1 (0.2–1.9)	0.5 (0.3–2.7)	.4060
CDAI at ABT introduction (median, IQR)	13.6 (9.9–22.6)	14.4 (8.8–23.2)	.8690
CDAI at 1 months (median, IQR)	8.4 (6.2–12.8)	9.6 (5.0–15.1)	.8256
CDAI at 3 months (median, IQR)	7.5 (4.1–11.4)	7.9 (4.5–11.7)	.9854
CDAI at 6 months (median, IQR)	6.1 (3.2–11.3)	5.9 (1.2–8.3)	.4110
CDAI at 12 months (median, IQR)	6.6 (3.9–8.9)	4.1 (0.7–7.6)	.0738
CDAI at 24 months (median, IQR)	4.8 (2.2–7.1)	3.1 (1.3–6.6)	.2058
CDAI at 36 months (median, IQR)	5.1 (20.–11.96)	3.5 (1.3–6.2)	.1612
Baseline TSS (median, IQR)	52 (19.5–205.5)	26.5 (4.0–83.2)	.0376
Baseline TSS $>$ 14	28 (85%)	18 (60%)	.0452
Steinblocker's roentgenograms stage	I: 15, II: 11, III: 7, IV: 0	I: 15, II: 11, III: 7, IV: 1	.2472
Interval of delta TSS assessment (month, median, IQR)	37 (35–42)	37 (34–39)	.6398
Delta TSS (median, IQR)	6 (2.7–11)	0 (0–1)	$<$.0001
Delta TSS/year (median, IQR)	2.0 (0.9–3.4)	0 (0–0.2)	$<$.0001

p-Values were calculated to compare the clinical characteristics of patients between patients who achieved estimated TSS REM or not. Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables. ABT: Abatacept, IQR: interquartile range; RF: Rheumatoid factor; ACPA: anti-cyclic citrullinated peptide antibodies; MTX: Methotrexate; GC: Glucocorticoid; b/tsDMARDs: biological or targeted synthetic DMARDs; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CDAI: clinical disease activity index; TSS: Total Sharp Score; estimated TSS REM: delta TSS/year $<$ 0.5.

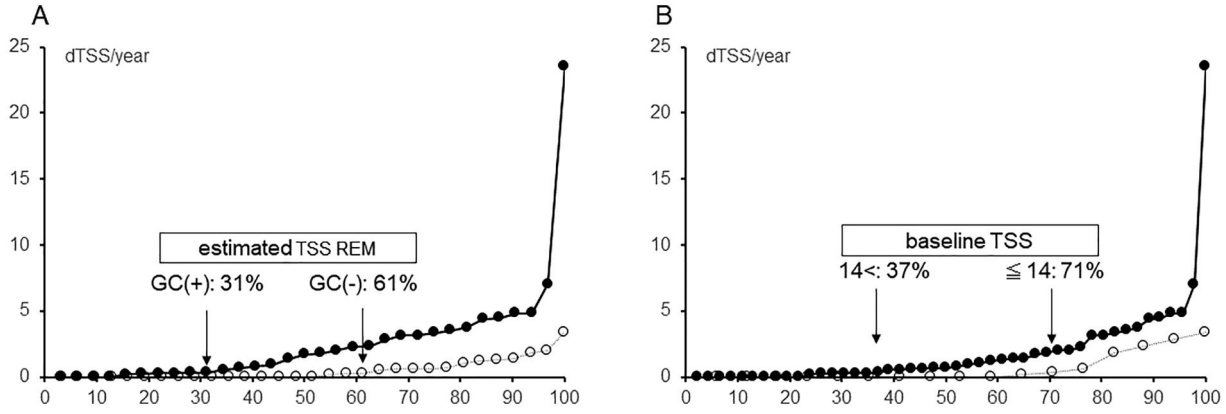

Figure 1. Cumulative probability plots of radiographic progression assessed by the modified. Total Sharp Score (mTSS/year). Patients who continued abatacept for more than 2 years were divided by concomitant glucocorticoid use (GC(+), $n = 31$) vs. not (GC(-), $n = 32$) (A) or divided by baseline total TSS was under 14 (≦14, $n = 17$) vs. over 14 (14<, $n = 46$).

3.3. Multivariate logistic analysis for long-term structural remission by ABT

Multivariate logistic regression analysis was performed to identify the factors associated with long-term structural remission (Table 3). Based on our clinical significance and results, sex, age at ABT induction, concomitant GC, and baseline TSS were employed in Model 1. The results showed that concomitant GC (risk ratio: 0.19, 95%CI: 0.06–0.64, $p = .0072$) was extracted as a significant negative predictor with structural remission. Even when concomitant GC, concomitant MTX use, history of b/tsDMARDs, and baseline TSS were included in Model 2, only concomitant GC was significant (risk ratio, 0.26; 95%CI: 0.08–0.79, $p = .0177$).

Table 3. Multivariate logistic analysis for long-term structural remission by abatacept.

	Model 1			Model 2		
	Risk ratio	95%CI	*p*-Value	Risk ratio	95%CI	*p*-Value
GC (on)	0.17	0.05–0.59	.0050	0.22	0.07–0.70	.0100
Sex (female)	0.3	0.06–1.44	.1328			
Age at ABT induction (/year)	1.01	0.95–1.07	.7841			
MTX (on)				1.45	0.46–4.60	.5253
History of b/tsDMARDs (used)				1.23	0.37–4.01	.7370
Baseline TSS (/unit)	0.99	0.99–1.0005	.0697	0.99	0.99–1.000023	.0508

p-Values were calculated as multivariate logistic regression analysis. GC: Glucocorticoid; ABT: Abatacept, MTX: Methotrexate; b/tsDMARDs: biological or targeted synthetic DMARDs; TSS: Total Sharp Score.

4. Discussion

In the present study, the long-term effects of ABT on radiological progression were evaluated, and multivariate analysis showed that concomitant GC use at baseline was the strongest negative predictive factor for estimated TSS REM.

First, the clinical characteristics of patients who continued ABT were elucidated. The patients were relatively older and had a lower CDAI after 12 months than those who dropped out, suggesting that patients and physicians should try not to stop ABT constantly. However, a relatively lower rate of estimated TSS REM was observed in the continued ABT group, partly because the other DMARDs were effective to clinical activities, which resulted in a greater effect in preventing radiographic progression. Furthermore, concomitant treatments initiated after discontinuation of ABT may have contributed to the prevention of radiographic progression, with 71% of cases receiving any b/tsDMARDs.

Few studies have reported on the long-term inhibitory effects of ABT on radiographic progression. By comparing the patients who achieved estimated TSS REM in the continued ABT group, it was revealed that concomitant GC was the strongest predictive factor in univariate or multivariate analysis. The therapeutic efficacy of GC in RA seems controversial since GC has anti-inflammatory effects but simultaneously induces osteoporosis. Several meta-analyses have shown that low-dose GC prevents joint destruction [15]. Nonetheless, the methodological contrast (utilizing Larsen scores as opposed to mTSS) could potentially account for the disparity observed in the present findings. Furthermore, none of the trials included in this meta-analysis extended beyond a duration of 3.5 years. In the present study, we suggest that GC may counteract the joint protective effects of ABT in its long-term continuation. From an osteoimmunological perspective, Lin Song's research revealed that T cells subjected to glucocorticoid (GC) treatment exhibit elevated steady-state levels of NF-κB receptor activator ligand (RANKL), which promotes the formation and maturation of osteoclasts and induces osteoporosis [16].

ACPA positivity is a poor prognostic factor for RA [2] and strongly correlates with joint destruction. However, in the present study, autoantibodies were not extracted to predict factors of joint destruction by long-term ABT therapies, partly because the patients' baseline TSS scores were over 50, which is considered an already progressive disease status.

This study had several limitations. First, this was a single-center retrospective study with a small sample size, which may introduce potential biases in the results. Second, this study did not consider why the patients decided to undergo ABT and could not compare the radiographic progression of long-term treatment with other b/tsDMARDs. Third, this study did not consider the ABT treatment period or the mode of administration (intravenous or subcutaneous injection). The potential for low adherence to bDMARADs can be observed in real-world situations.

Despite the limitations stated above, it can be concluded that in patients treated with ABT for more than 2 years, concomitant GC is a relatively strong risk factor for joint destruction. Therefore, physicians should consider combination therapy when initiating ABT to prevent future joint damage.

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Authors' contributions

KMurakami, RW, HI, KMurata, TFujii, HO, AO, MT, AM, and MH provided patient care. TFujisaki supported the evaluation of X-rays. WY supported the data collection. RW drafted the manuscript. All the authors have read and approved the final version of the manuscript.

Disclosure statement

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