Clinical, radiographic and functional efficacy of abatacept in routine care for rheumatoid arthritis patients: Abatacept Leading Trial for RA on Imaging Remission (ALTAIR) study

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Abstract

Objective

To investigate the efficacy and safety of abatacept for treating patients with rheumatoid arthritis (RA) in routine clinical practice and to determine the prognostic factors affecting clinical outcomes.

Methods

We performed a retrospective study of 194 RA patients treated with abatacept. Clinical outcomes at 1 year after the treatment were assessed. Joint damage was assessed by the van der Heijde-modified total Sharp score (mTSS).

Results

Of the 194 patients, abatacept was discontinued in 51 patients, resulting in a retention rate at week 52 of 73.7%. At week 52, 23.7% of patients achieved clinical remission (SDAI ≤3.3). Lower SDAI and higher RF titre at baseline were the prognostic factor for SDAI at 52 weeks. Structural remission (ΔmTSS ≤0.5) was achieved in 73.4% of patients. However, clinical relevant radiographic progression which was defined as an increase in ΔmTSS >3 in a year, occurred in 7.6% of patients. Likewise, rapid radiological progression, which was defined as an increase in ΔmTSS >5 in a year, was observed in 6.4% of patients. 16.5% of patients achieved comprehensive disease remission, which was defined as SDAI ≤3.3, HAQ-DI ≤0.5, ΔmTSS ≤0.5, while 22.4% of patients achieved comprehensive disease control (CDC), which was defined as SDAI ≤11.0, HAQ-DI ≤0.5, ΔmTSS ≤0.5.

Conclusion

The present results confirm that abatacept is effective and safe in routine clinical practice. It is possible that abatacept is more effective in seropositive RA patients with significant immunological abnormality.

Key words

abatacept, rheumatoid arthritis, structural remission, comprehensive disease remission, van der Heijde-modified total Sharp score

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Introduction

With the development of biologic agents targeting pro-inflammatory cytokines, clinical remission has become a primary goal in the treatment of rheumatoid arthritis (RA). Moreover, structural and functional remission has become possible (1). Inflammatory cells [*e.g.* macrophages] and pro-inflammatory cytokines [*e.g.* tumour necrosis factor (TNF) and interleukin (IL)-6 produced by synovial fibroblasts] play important roles in RA pathogenesis. RA treatments targeting T cells have also been a focus of research, based on the results of a study showing the infiltration of numerous CD4-positive T cells and expression of major histocompatibility complex (MHC) class II molecules in the synovial membrane (2). Another study showed a strong correlation between RA and the major histocompatibility antigen, human leukocyte antigen (HLA)-DR4 (3), whereas a more recent study revealed the importance of T-helper cells (Th)17 in RA (4).

In addition to TNF inhibitors, the safety and effectiveness of abatacept, which prevents T-cell activation via selectively targeting the interaction of CD80/86 with CD28, have been established in multiple clinical studies (5-9). The clinical efficacy was maintained over the long term, coupled with consistent safety and tolerability (10). The HAQ reduction appeared equally among biologics by indirect comparison (11). Moreover, abatacept demonstrated efficacy in amyloid A amyloidosis secondary to RA (12) and could modulate endothelial function via alternations in classical cardiovascular disease risk factors (13). The 2013 Recommendations for RA Treatment recommend the use of abatacept as a first-line biologic along with anti-TNF inhibitors (14). The next issue is how to use these biological products differently (15).

Randomised controlled trials (RCTs) are regarded as a reliable approach to obtain evidence on the efficacy and safety of drugs, and the results of these trials often lead to the approval of new drugs. However, there are limitations to RCTs (16). The most important limitation is that the study subjects are selected using inclusion and exclusion criteria. In most cases, older and young individuals and those with common medical conditions (*e.g.* liver and/or renal disease) are excluded. Such exclusions may impair the generalisability of results (17). This limits the applicability of the results on the efficacy and safety of drugs to clinical practice. Although numerous pre-marketing studies of abatacept have been performed, very few studies have been evaluated with its efficacy for treating patients with RA in the context of actual clinical practice (18, 19). Moreover, there are no reports investigated the efficacy of abatacept on joint damage progression for 1 year in actual clinical practice settings.

Therefore, this study, the Abatacept Leading Trial for RA on Imaging Remission (ALTAIR), was conducted to investigate the inhibitory effects of abatacept on joint damage and its clinical efficacy and safety in routine clinical practice. We also sought to identify possible predictors of response.

Patients and methods

Patients

This was an open-label, non-randomised, observational and retrospective study involving RA patients (n=194). All patients who started treatment with abatacept between November 2010 and November 2013 at our hospital were registered in the study. All patients had a diagnosis of RA defined using the American Rheumatism Association 1987 Revised Criteria or the 2010 ACR-EULAR classification criteria (20-22). The study was approved by the ethics review board of the University of Occupational and Environmental Health, Japan and was conducted as a retrospective observation study using anonymised data. Abatacept were used within the health insurance coverage for RA in Japan. This study was registered with the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/) (UMIN000008285).

Abatacept and Tocilizumab treatment

Abatacept was prescribed to patients with RA uncontrolled by normal doses of existing disease-modifying anti-rheumatic drugs (DMARDs). Patients

Table I. Baseline characteristics of patients.

Variables	Total (n = 194)
Age (years)	63.0 ± 14.6
Gender, n (% female)	166 (85.6)
Disease duration (years)	9.6 ± 11.0
Stage (I/II/III/IV %)	(17.1/39.9/24.9/18.1)
Class (I/II/III/IV %)	(1.6/79.3/18.7/0.5)
Prior use of biologics, n (%)	95 (48.5)
RF positive, n (%)	151 (77.8)
MTX use, n (%)	136 (70.1)
MTX dose (mg/week)	11.7 ± 3.6
Oral steroid use, n (%)	47 (24.2)
Oral steroid use (mg/day*)	4.9 ± 5.3
MMP-3 (ng/mL)	175.3 ± 162.7
SJC, 0-28	6.1 ± 4.7
TJC, 0-28	8.0 ± 6.2
ESR (mm/h)	45.4 ± 30.4
CRP (mg/dL)	1.5 ± 2.2
GH, VAS 0-100 mm	56.7 ± 23.8
SDAI	26.0 ± 12.4
CDAI	24.4 ± 11.7
DAS28-ESR	5.3 ± 1.2
HAQ-DI	1.5 ± 0.8
mTSS	61.1 ± 92.6
Median (IQR)	17.5 (4.5-80.5)
Estimated YP (DTSS)	8.6 ± 12.5
Median (IQR)	4.5 (1.6-10.6)

Mean ± SD unless otherwise indicated. RF: rheumatoid factor; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GH: patient's global assessment of disease activity; VAS: visual analogue scale; DAS: disease activity score; mTSS: modified total Sharp score; YP: yearly progression; IQR: interquartile range.
*Prednisolone equivalents.

Suppl. Table 1 (SI).
Reason for discontinuation.

Variables	All (n=194)
Total	51 (26.3%)
Lack of efficacy	35 (18.0%)
Adverse events	6 (3.1%)
Other reasons	10 (5.2%)

received a fixed dose of abatacept of about 10 mg/kg body weight; patients weighing <60 kg received 500 mg of abatacept, those weighing 60-100 kg received 750 mg, and those weighing >100 kg received 1000 mg. Abatacept was administered in a 30-min intravenous infusion at Weeks 0, 2, and 4, and then every 4 weeks thereafter. Alternatively, 125 mg abatacept administered subcutaneous weekly.

Clinical efficacy

Disease activity was assessed using the Simplified Disease Activity Index (SDAI) (23, 24)and the 28-joint Disease Activity Score (DAS28)-ESR (25), which were calculated as previously described. Disability was assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI) (26). Joint damage was assessed by the van der Heijde-modified total Sharp score (mTSS) (27). Two expert readers independently scored articular damage and progression in a blinded fashion according to the mTSS scoring methods. Radiographs of hands and feet were obtained at baseline, week 24 and week 52 for patients who completed the study or at discontinuation.

Statistical analysis

Patient baseline characteristics are summarised as the mean and standard deviation (SD), with percentiles for the overall patient population. The last observation carried forward (LOCF) method was used for patients who discontinued before week 52 to include all patients in analyses. For changes in radiographic end point, linear extrapolation was used for missing values. Kaplan-Meier analysis was used to assess the rate of abatacept retention. The improvements in SDAI, HAQ-DI and Δ mTSS scores from baseline to week 52 were analysed using the paired *t*-test. Stepwise multiple regression analysis was performed to determine prognostic factors. The optimal cut-off value for the subgroup analysis was calculated using receiver operator characteristic (ROC) curve analysis. All reported *p*-values are two-sided and not adjusted for multiple testing (28, 29). The level of significance was taken as $p<0.05$.

Results

Baseline characteristics of patients

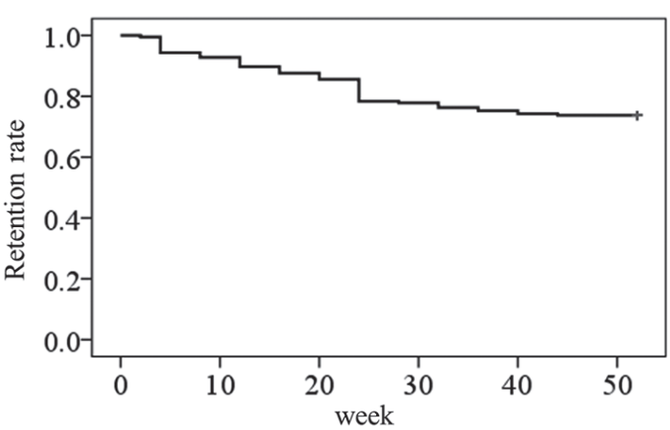
We retrospectively analysed data on 194 patients who were treated with abatacept between 2010 and 2013. The mean age of the patients was 63.0 years, and 85.6% were female (Table I). The mean disease duration was 9.6 years, and mean disease activity at baseline was 26.0 and 5.3 for SDAI and DAS28-ESR, respectively. Mean HAQ-DI was 1.5. Overall, 48.5% patients were biologic-experienced. MTX was concomitantly administered in 70.1% patients, with a mean dose of 11.7 mg/week. Glucocorticoids were used concomitantly in 24.2% patients, with a mean dose of 4.9 mg/day (prednisolone equivalents) (Table I). Other laboratory findings included rheumatoid factor (RF) positivity in 77.8%, with mean matrix metalloproteinase (MMP)-3, ESR, and C-reactive protein (CRP) levels of 175.3 ng/mL, 45.4 mm/h, and 1.5 mg/dL, respectively.

Retention rate and adverse events

Of the 194 patients included in this study, abatacept therapy was discontinued in 51 patients, resulting in a retention rate at week 52 of 73.7% (Suppl. Fig. 1). Reasons for discontinuing abatacept were lack of efficacy (18.0%), adverse events (3.1%), or another reason (5.2%) (Suppl. Table I). Of note, only 0.5% patients withdrew because of infection.

Efficacy of abatacept

The time course of SDAI recorded over 52 weeks is shown in Figure 1A. The mean SDAI score among all 194 pa-



Suppl. Fig. 1. Retention rate of abatacept treatment over 52 weeks (Kaplan-Meier plots). At week 52, 73.7% of 194 patients.

tients decreased significantly from 26.0 at baseline to 12.3 at week 24, 12.2 at week 52. Changes in disease activity in patients stratified by SDAI (high, SDAI >26; moderate, 26 ≥SDAI >11; low, 11 ≥SDAI >3.3; and remission, SDAI ≤3.3) are shown in Figure 1B. At week 24, 16% of patients achieved clinical remission and 24% of patients achieved clinical remission at week 52. Overall, 56% patients achieved either remission or a low disease activity at the end of this study.

HAQ-DI scores in all 194 patients decreased significantly from 1.5 at baseline to 1.2 at week 24, 1.2 at week 52 (Fig. 1C). The functional remission rate (*i.e.* HAQ-DI ≤0.5) increased from19% at baseline to 31% at week 24, to 34% at week 52 (Fig. 1D).

The mean ΔmTSS improved significantly from 8.4 at baseline to 1.1 at week 24, 1.1 at week 52 (Fig. 1E). Figure 1F shows a cumulative scatterplot of ΔmTSS at week 52. The structural remission (defined as ΔmTSS score ≤0.5) was achieved in 73.7% of patients. However, clinical relevant radiographic progression (CRRP), which was defined as an increase in ΔmTSS >3 in 1 year (30), occurred in 7.6% of patients. Likewise, rapid radiological progression(RRP) , which was defined as an increase in ΔmTSS >5 in 1 year (31), was observed in 6.4% of patients.

Predictors for SDAI, HAQ-DI andΔmTSS

We next determined the prognostic factors contributing SDAI, HAQ andΔmTSS at week 52. Multiple regression analysis of SDAI showed that baseline SDAI (correlation coefficient = 0.52, $p<0.001$) and baseline titre of RF (correlation coefficient = -0.13, $p=0.05$)

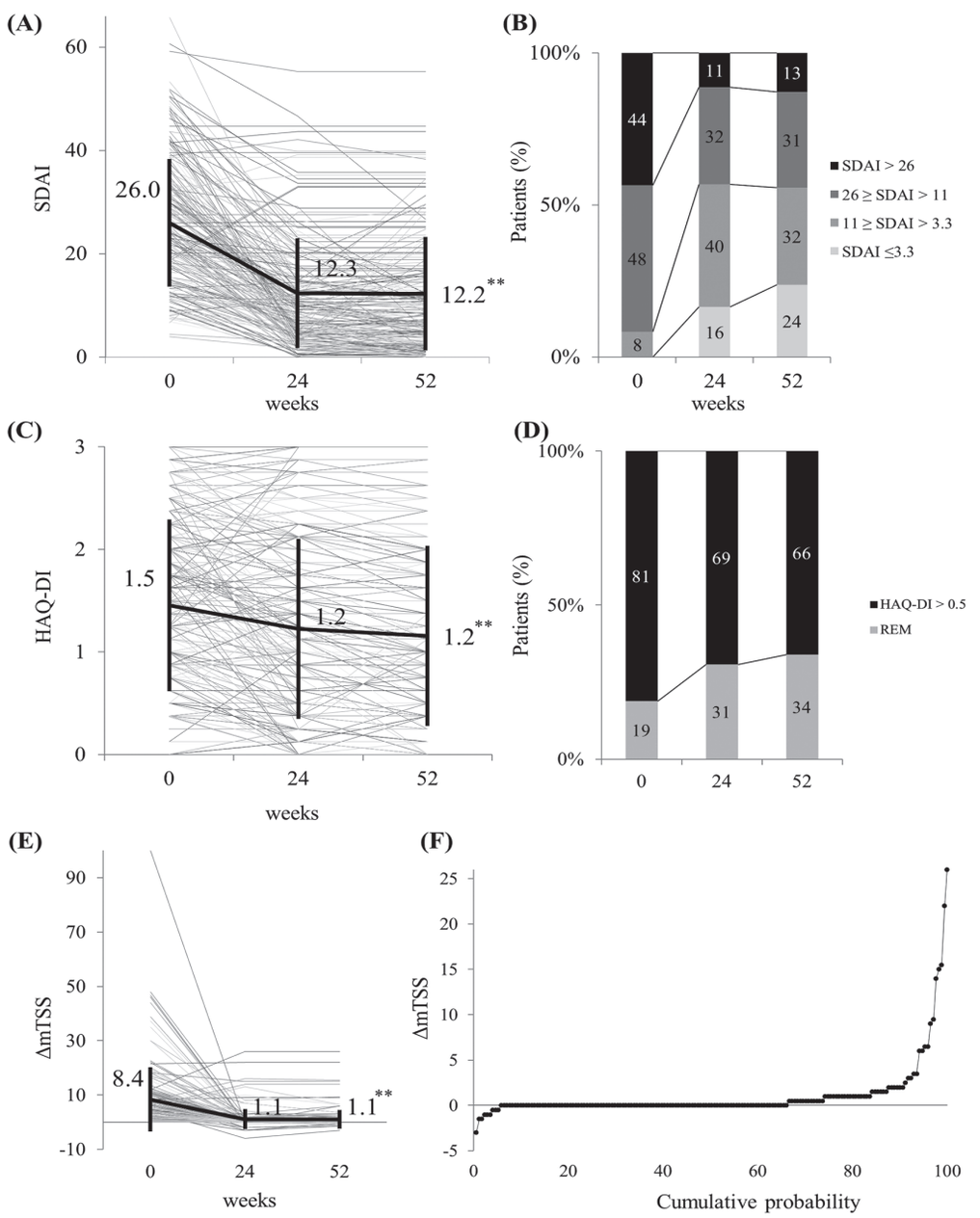


Fig. 1. Effect of treatment with abatacept for 52 weeks on:
A: time course of SDAI,
B: proportion of patients with disease activity,
C: time course of HAQ-DI,
D: proportion of patients with HAQ-DI >0.5,
E: time course of yearly progression in mTSS, and
F: Cumulative probability for a change in mTSS from base line. Date were analysed by the last observation carried forward (LOCF) method.
$^{**}p<0.01$

were significantly associated with SDAI after 52 weeks of treatment (Table II). These results indicated that higher titres of RF and lower SDAI were associated with lower SDAI at week 52 in patients treated with abatacept.

Based on these results, we determined the optimal cut-off value for baseline RF titre using receiver operating characteristic (ROC) curve analysis. This analysis yielded a cut-off value of RF ≥50 U/mL for SDAI remission. When we evaluated disease activity according to RF titre of 50 U/mL, although the SDAI score decreased significantly from baseline to week 52 in both patients with RF ≥50 U/mL and patients with RF <50 U/mL, we found that the magnitude of improvement was significantly greater in patients with RF ≥50 (Fig. 2A). In addition, the decreases of RF titer correlated with the improvement of SDAI among all 194 patients (Fig. 2B), which indicate that abatacept may improve the disease activity with the correction of immunological abnormalities.

Similarly, multiple regression analysis of HAQ-DI showed that previous use of a biologic agent (correlation coefficient = 0.10, p=0.03), baseline HAQ-DI (correlation coefficient = 0.70, p<0.001), and baseline mTSS (correlation coefficient = 0.12, p=0.01) were significantly associated with HAQ-DI at week 52 (Table II). These results indicate that patients with advanced joint damage and higher HAQ-DI at the start of abatacept treatment are less likely to achieve significant improvements in functional impairment.

ROC curve analysis yielded an optimal cut-off mTSS value of 36 for functional remission. At week 52, the percentage of patients with functional remission was 45% among patients with baseline mTSS <36, compared with 20% among patients with baseline mTSS ≥36 (Fig. 2C).

Finally, multiple regression analysis of ΔmTSS revealed that baseline CRP level (correlation coefficient = 0.27, p<0.001) was significantly associated with ΔmTSS after 52 weeks of treatment of abatacept (Table II).

ROC curve analysis yielded an optimal cut-off CRP level of 1.3 mg/dl for structural remission. At week 52, the probability plots in patients with CRP <1.3mg/dl and patients with CRP ≥1.3mg/dl are shown in Figure 2D. Structural remission was achieved in 83.8% of patients with CRP <1.3mg/dl and in 55.0% of patients with CRP ≥1.3 mg/dl. Moreover, CRRP and RRP were occurred in 5.4% and 3.6% of patient with CRP <1.3mg/dl, respectively, whereas CRRP and RRP were occurred in 10.0% and 11.7% of patient with CRP ≥1.3mg/d, respectively.

Table II. Independent predictors for SDAI, HAQ-DI and ΔmTSS at week 52 in multivariable analysis.

Variables	SDAI at week 52		HAQ-DI at week 52		ΔmTSS at week 52	
	regression coefficient	p-value	regression coefficient	p-value	regression coefficient	p-value
Age	-0.02	0.78	0.09	0.07	-0.07	0.34
Sex (female)	0.07	0.30	0.07	0.17	0.07	0.33
Disease duration	0.02	0.80	0.05	0.43	0.00	0.97
Prior use of biologics	0.12	0.06	**0.10**	**0.03**	0.06	0.42
MTX use	-0.02	0.79	-0.05	0.27	0.13	0.07
Oral steroid use	0.08	0.20	0.02	0.67	0.00	0.99
CRP (at baseline)	0.08	0.25	-0.04	0.43	**0.27**	**0.00**
RF titre (at baseline)	**-0.13**	**0.05**	-0.07	0.11	-0.05	0.49
MMP-3 (at baseline)	-0.02	0.78	-0.01	0.89	-0.03	0.73
SDAI (at baseline)	**0.51**	**0.00**	0.03	0.57	0.04	0.59
HAQ-DI (at baseline)	0.07	0.32	**0.70**	**0.00**	0.00	0.99
mTSS (at baseline)	0.00	0.99	**0.12**	**0.01**	0.06	0.41

Comprehensive disease remission and control

Not only clinical remission, but also structural remission and functional remission have been perceived as an appropriate and realistic primary goal in many patients (32). In recent years, the importance of comprehensive disease remission (CDR) according to triple criteria [clinical remission (SDAI ≤3.3), normal function (HAQ ≤0.5), and radiographic nonprogression (ΔmTSS ≤0.5)] and comprehensive disease control (CDC) according to triple criteria [low disease activity (SDAI ≤11), normal function, and radiographic nonprogression] have been known (33). At week 52, 16.5% and 22.4% of patients treated with abatacept achieved CDR and CDC, respectively (Fig. 3A).

Multivariate logistic regression analysis was performed to investigate factors related to achievement of CDR and CDC at week 52. SDAI (odds ratio = 0.01, p=0.02) and HAQ-DI (odds ratio = 0.04, p=0.02) had marked correlation with CDR achievement and age (odds ratio = 0.08, p=0.02) and HAQ-DI (odds ratio = 0.05, p=0.01) had marked correlation with CDC achievement (Table III). Subsequent ROC curve analysis yielded an optimal cut-off age of 49 years old for CDC achievement. At week 52, the percentage of patients with CDC was 57.7% among patients less than 49 years old, compared with 15.9% among patients over 49 years old (Fig. 3B).

Discussion

The ALTAIR study evaluated the efficacy and safety of abatacept over a period of 52 weeks in 194 RA patients treated with abatacept in Japan.

The inhibitory effects of abatacept on joint damage have been demonstrated in four RCTs (9, 34-36). However, the results of RCTs are not always applicable to daily clinical practice since the characteristics of patients entering the trials are largely determined by the inclusion/exclusion criteria (16). Therefore, observational studies (non-RCTs) provide a valuable supplement to the RCTs. To the best of our knowledge, there are only two reports to investigate the efficacies of abatacept of joint damage for 24 weeks (18, 19). We investigated, for the first time, the efficacy of abatacept on joint damage progression for 1 year in actual clinical practice settings.

Structural remission, corresponding to inhibition of joint damage progression, was achieved in approximately 73.4% of patients treated with abatacept for 52 weeks. On the other hand, CRRP was observed 7.6% of patients and RRP was observed 6.4% of patients, respectively. This analysis revealed that only CRP

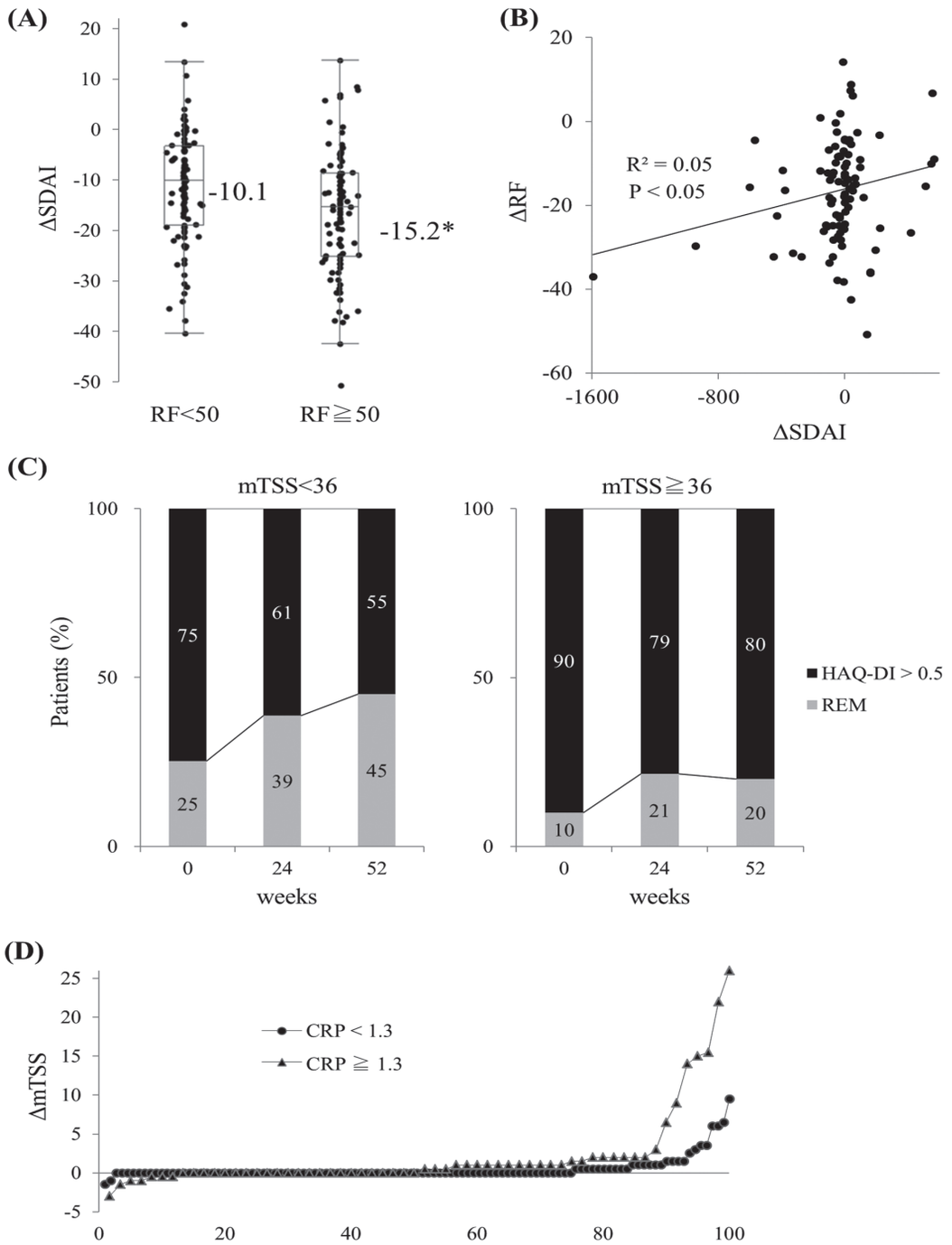


Fig. 2. Subgroup analysis for SDAI, HAQ-DI and yearly progression in mTSS. Date were analysed by the last observation carried forward (LOCF) method.
A: Delta SDAI at 52 weeks stratified by baseline RF (<50 *vs*. ≥50 U/mL),
B: Relationship between delta SDAI and delta RF,
C: Time course of the percentage of functional remission using HAQ-DI stratified by mTSS at baseline (<36 *vs*. ≥36),
D: Cumulative probability distribution of change in two groups. In 93 out of the 111 patients (83.8%) with CRP <1.3mg/dl and in 33 out of the 60 patients (55.0%) with CRP ≥ 1.3mg/dl at baseline, the yearly progressions was ≤0.5, respectively.

level was significantly associated with ΔmTSS after 52 weeks of treatment with abatacept. Unexpectedly, SDAI, MMP-3 and mTSS were not associated with joint damage progression after treatment of abatacept. These results were consistent with previous cohort, which is based on 50 RA patients for 24 weeks (18). Moreover, the subgroup analysis according to the CRP cut-off value of 1.3 mg/dl, which was determined by ROC curve analysis, revealed very high proportion of patients with CRP <1.3 mg/dl achieved structural remission (83.8%). Of note, the proportion of CRRP (5.4%) and RRP (3.6%) were also decreased in patients with CRP <1.3 mg/dl. These results may attributable to the biologic properties of abatacept, which do not directly block pro-inflammatory cytokines signaling and inhibit osteoclast differentiation via binding the osteoclast precursor cells directly (37, 38).

In the present study, the clinical remission rate and the percentages of patients with low disease activity after 52 weeks of abatacept therapy, based on SDAI, were assessed. Our results showed that the clinical remission rates of abatacept were 16.5% at week 24, and 23.7% at week 52. Overall, 55.7% patients achieved either remission or a low disease activity at week 52. In this study, lower SDAI and higher RF titre were significantly associated with the SDAI

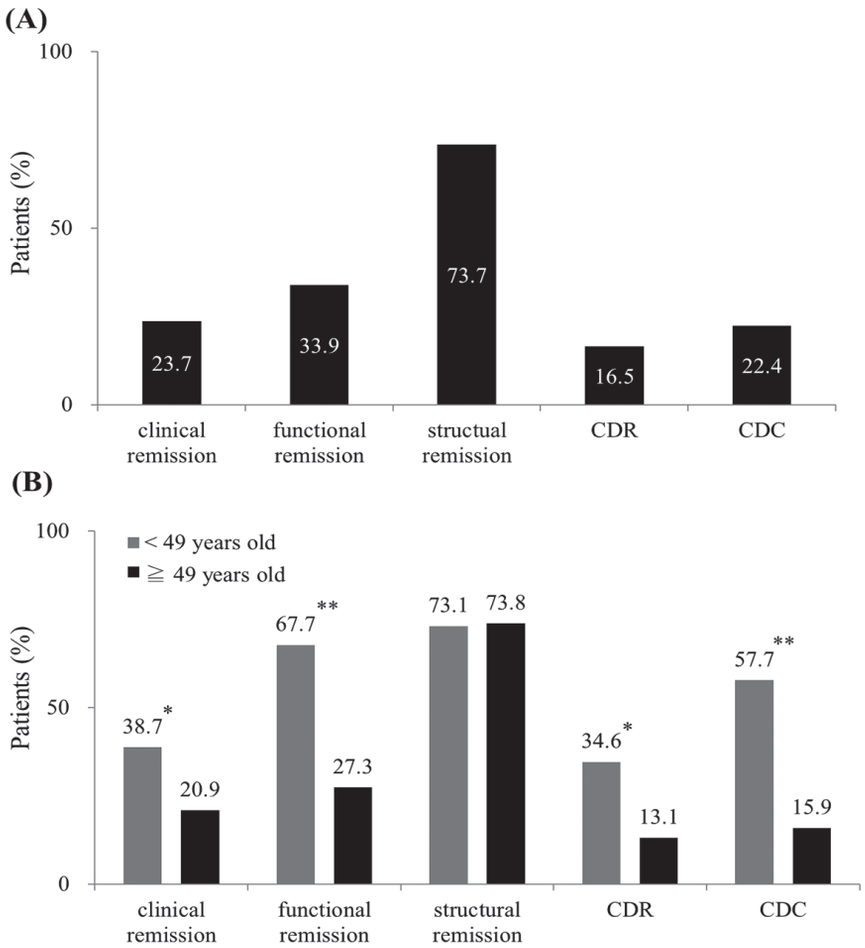


Fig. 3. Rate of comprehensive disease remission and control.
A: Proportion of patients with each remission at 52 weeks. **B**: Subgroup analysis for clinical, functional, structural and comprehensive disease remission (CDR) and comprehensive disease control (CDC) stratified by patients' age (<49 vs ≥49 years old). *p<0.05 and **p<0.01.

Table III. Independent predictors for comprehensive disease remission (CDR) and control (CDC) at week 52 in logistic regression.

Variables	CDR at week 52		CDC at week 52	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age	0.39 (0.03-4.37)	0.44	0.08 (0.1-0.66)	**0.02**
Sex (female)	1.08 (0.25-5.26)	0.92	0.98 (0.26-4.01)	0.98
Disease duration	0.01 (0.00-1.24)	0.09	0.02 (0.00-1.46)	0.10
Prior use of biologics	1.07 (0.36-3.21)	0.9	1.44 (0.55-3.81)	0.46
MTX use	2.15 (0.61-7.61)	0.23	1.43 (0.45-4.39)	0.53
Oral steroid use	1.14 (0.31-4.89)	0.85	0.91 (0.29-2.98)	0.87
CRP (at baseline)	163.87 (0.62-33703.40)	0.06	10.02 (0.10-782.76)	0.30
RF titre (at baseline)	0.17 (0.00-18.69)	0.55	2.28 (0.06-78.85)	0.64
MMP-3 (at baseline)	0.22 (0.01-3.23)	0.30	1.2 (0.11-11.70)	0.88
SDAI (at baseline)	**0.01 (0.00-0.39)**	**0.02**	0.03 (0.00-0.89)	0.05
HAQ-DI (at baseline)	**0.04 (0.00-0.52)**	**0.02**	**0.05 (0.00-0.49)**	0.01
mTSS (at baseline)	2.11 (0.00-421.33)	0.81	2.08 (0.01-144.39)	0.76

at week 52. It was reported that, unlike TNF inhibitors, abatacept has strong therapeutic effects in anti-CCP antibody-positive patients (39), and patients with higher RF titres were shown to respond well to rituximab (40, 41). Thus, it seems likely that this may be a characteristic of targeting T cells or B cells, and abatacept are more effective in seropositive RA patients. Moreover, there were positive correlation between the decrease of RF titre and the improvement of SDAI in this study. These results suggest that abatacept may provide decrease of the disease activity along with improvement of the pathological condition caused by immune abnormality.

Multivariate analysis revealed that baseline HAQ-DI and baseline mTSS were significantly associated with HAQ-DI scores, as a measure of functional remission at week 52. These results indicate that patients with advanced joint damage at the start of abatacept treatment already have damage related physical disability (42).

Over 52 weeks of treatment, 23.7%, 73.7%, and 33.9% of patients achieved clinical remission, structural remission, and functional remission. Moreover, CDR, which include a set of criteria addressing each of the treatment goals for RA (33), was achieved by 16.5% of patients. Likewise, CDC was achieved by 22.4% of patients. The present study also showed that patient's age was the prognostic factor contributing to the achievement of CDC (odds ratio = 0.08, p=0.02). In fact, 57.7% of the patients less than 49 years old was achieved CDC, while 15.9% of the patients over 50 years old was achieved CDC. Previous report showed higher safety of abatacept rather than other biologics agents (43), and abatacept has tended to be used for the elderly. However, the efficacy in people aged less than 49 years old was confirmed in terms of the achievement of CDR and CDC.

The limitation of this study was that this was conducted as a retrospective observational study without a formal control group and it was impossible to compare with other biologics.

In conclusion, the present study demonstrates that abatacept inhibited progression of joint damage in actual clinical practice. Furthermore, as abatacept targets activated T cells, the results of the present study support the use of abatacept for seropositive RA patients with significant immunological abnormality. We believe that these clinical evidences based on the observation study lead to the development of personalised treatment using biological products for patients with RA.

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