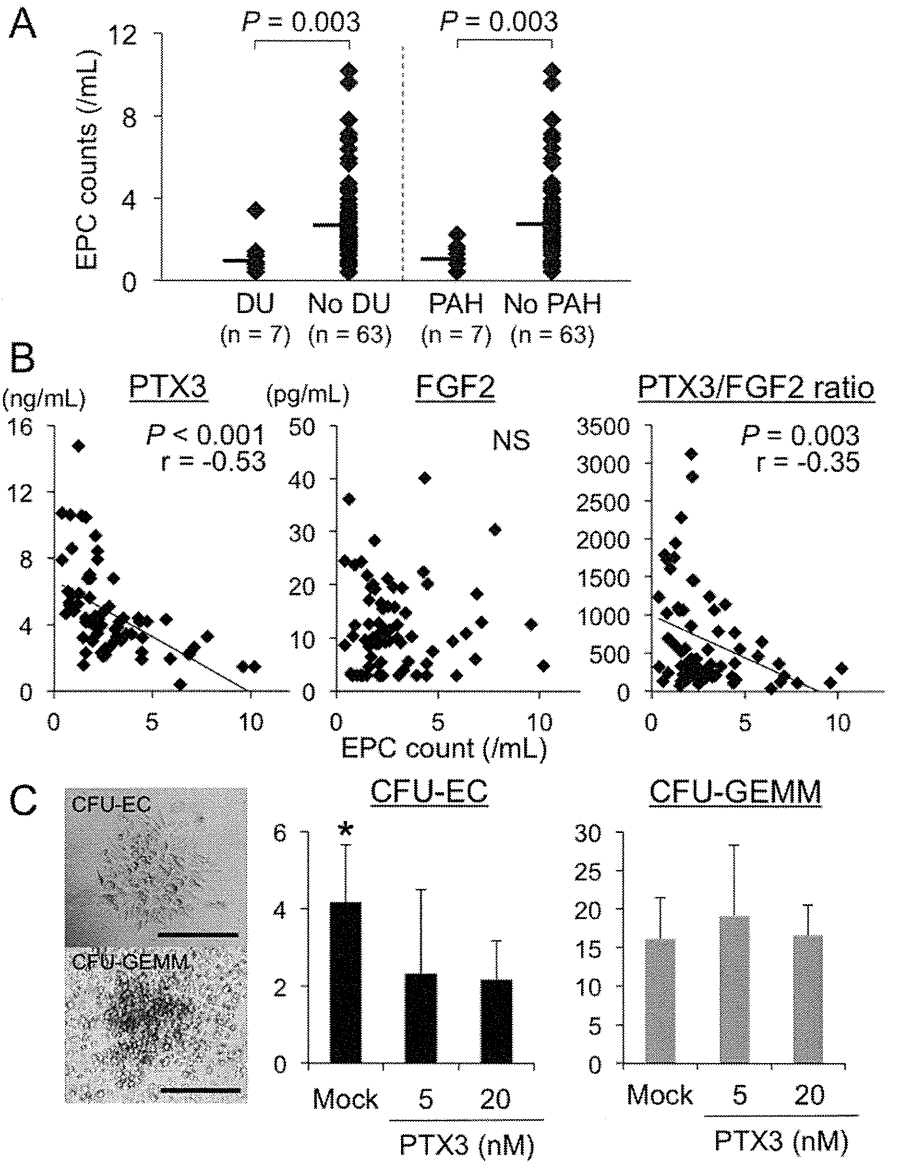

Figure 5. Relationship between endothelial progenitor cell (EPC) counts and concentration of circulating PTX3 in SSc patients. **A,** EPC counts in SSc patients stratified by the presence or absence of digital ulcers (DU) or pulmonary arterial hypertension (PAH). Symbols represent individual patients; bars show the mean. *P* values were determined by Mann-Whitney U test. **B,** Correlation between EPC counts and concentrations of PTX3 or FGF-2 in the circulation or between EPC counts and the PTX3:FGF-2 ratio. Symbols represent individual patients. **C,** Effect of PTX3 on in vitro EPC differentiation. Mouse bone marrow mononuclear cells were cultured under proangiogenic conditions in the presence or absence (mock) of PTX3. Left, Images showing typical morphology of colony forming unit–endothelial cell (CFU-EC) colonies and CFU–granulocyte–erythrocyte–macrophage–megakaryocyte (GEMM) colonies. Bars = 0.2 mm. Middle and right, Effect of PTX3 on formation of CFU-EC colonies (middle) and CFU-GEMM colonies (right). Values are the mean ± SD of 10 independent measurements. * = $P = 0.01$ versus 5 n*M* of PTX3 and $P = 0.005$ versus 20 n*M* of PTX3. See Figure 1 for other definitions.

PTX3 in the circulation in the context of the occurrence of digital ulcers or PAH.

Inhibition of EPC differentiation by PTX3. To investigate the effect of PTX3 on EPC differentiation, we used an in vitro mouse system in which nonadherent bone marrow mononuclear cells were cultured under EPC differentiation conditions (which included FGF-2) in the presence or absence of PTX3, followed by colony-

forming assays to count CFU-EC and CFU-GEMM colonies (Figure 5C). In these cultures, PTX3 reduced the formation of CFU-EC colonies to approximately half, but had no effect on CFU-GEMM colony formation. Further increases in the concentration of PTX3 did not increase the inhibitory effect. This suggests that an FGF-2–independent pathway is also involved in this in vitro EPC differentiation, since PTX3 is known to directly inhibit binding of FGF-2 to its receptor (5). Thus, exposure to high concentrations of PTX3 may suppress EPC differentiation, leading to a negative correlation between PTX3 levels and EPC counts.

DISCUSSION

In this study, we found that circulating PTX3 was elevated in SSc patients, irrespective of the disease subset. Interestingly, elevated PTX3 levels were associated with vascular manifestations such as digital ulcers and PAH, but not with the fibrotic aspects of the disease. This was confirmed by multivariate analysis, in which PTX3 was identified as an independent parameter for the presence of digital ulcers and PAH. Elevated PTX3 was also identified as a good predictor for the future development of digital ulcers. Together, these findings suggest that PTX3 primarily promotes SSc vasculopathy, which is consistent with previous studies (6,26). However, while Iwata and colleagues also found correlations between elevated PTX3 and various fibrotic aspects of SSc, including dcSSc, high MRSS, pulmonary fibrosis, and heart involvement, they did not find a correlation with PAH (6). Although the exact reasons for this discrepancy are uncertain, it may be due to differences in the methods of measuring PTX3 levels and the definitions for the involvement of various organs, as well as the lower proportion of patients with dcSSc in our study. Since circulating PTX3 levels stayed fairly stable over the course of this study, PTX3 should prove to be a useful biomarker for the future development of digital ulcers in SSc patients.

Since PTX3 exerts its antiangiogenic effects primarily by competing with FGF-2 for binding to its receptor, for which PTX3 has higher affinity (5), the balance between circulating PTX3 and FGF-2 can reasonably be used to assess net anti/proangiogenic activity. Since FGF-2 was also elevated in SSc patients compared to healthy subjects, as other studies have also shown (27,28), the PTX3:FGF-2 ratio remained comparable between SSc patients and healthy controls. However, as with PTX3, our results clearly identified the PTX3:FGF-2 ratio as an independent parameter for the presence of digital ulcers and PAH, as well as a predictor for the future development of digital ulcers.

The roles of FGF-2 in neovascularization are mediated in part by the promotion of angiogenesis, a process in which ECs proliferate and sprout from preexisting vessels (29,30). It has been suggested that chronic tissue ischemia and a lack of compensatory angiogenesis lead to vascular manifestations in SSc patients (31). In this regard, the angiogenic capacity of ECs derived from SSc skin was reduced by FGF-2 and VEGF in vitro (9). On the other hand, we have proposed that vasculogenesis, a vascularization process that involves the recruitment and in situ differentiation of bone marrow–derived EPCs, is also defective in SSc patients (32); this is based on the reduced counts and impaired differentiation potential of EPCs in SSc (19,33). However, the underlying mechanisms of defective vasculogenesis in SSc are not well understood. In our present study, we showed that EPC counts were inversely correlated with the level of circulating PTX3 or the PTX3:FGF-2 ratio, and that PTX3 could inhibit differentiation of stem cells into EPCs in in vitro cultures with FGF-2. Therefore, it is likely that exposure to a high concentration of PTX3 suppresses the FGF-2–mediated processes in both angiogenesis and vasculogenesis, increasing the risk of digital ulcers and PAH, although we did not show direct evidence of an inhibitory effect of PTX3 on FGF-2 in our assay system.

While elevated PTX3 was associated with both digital ulcers and PAH, SSc patients with PAH uniquely exhibited FGF-2 levels similar to those in healthy controls. This suggests that digital ulcers and PAH, in part, have distinct pathogenic processes in SSc. In this regard, investigators studying patients from French and Canadian registries reported that the occurrence of digital ulcers did not necessarily correlate with that of PAH (22,23), but the use of pulmonary vasodilators in patients with PAH may prevent the onset of digital ulcers. On the other hand, the relatively normal FGF-2 levels seen in patients with SSc-associated PAH contrasts sharply with the elevated FGF-2 seen in patients with idiopathic PAH (34), and cultured pulmonary ECs derived from patients with idiopathic PAH also overexpress FGF-2 (35). Furthermore, a series of studies using animal models for medial hypertrophy of the pulmonary arterioles showed that FGF-2 expression is enhanced in pulmonary arterioles, and that knocking down FGF-2 or administering FGF receptor antagonists reverses pulmonary vascular remodeling (35–37).

Differences in FGF-2 behavior in SSc-associated PAH and idiopathic PAH may be responsible for the

distinct pulmonary vascular histologic features seen in these 2 conditions. Specifically, SSc-associated PAH is characterized by intimal fibrosis of the pulmonary arterioles and venules (pulmonary venoocclusive disease–like changes) and the absence of the plexogenic arteriopathy that is typical of idiopathic PAH (38). Comprehensive gene expression profiling of lung samples showed that SPARC and thrombospondin 1 are up-regulated in patients with SSc-associated PAH in comparison with those with idiopathic PAH (39). Interestingly, these molecules are known to suppress autocrine and paracrine FGF-2 production loops (40,41). Therefore, it is likely that levels of FGF-2 signaling in the pathogenic process of PAH modify pulmonary vascular remodeling.

In summary, circulating PTX3 was elevated in SSc patients and was a useful biomarker predicting the presence of digital ulcers and PAH as well as the future development of digital ulcers. In addition, PTX3 may contribute to SSc vasculopathy by inhibiting vasculogenesis-mediated neovascularization through its suppressive effects on FGF-2. Further studies are necessary to elucidate these roles and the complex interactions of anti/proangiogenic factors in the development of vascular manifestations of SSc.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kuwana had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Shirai, Tamura, Kuwana.

Acquisition of data. Shirai, Okazaki, Inoue, Tamura, Yasuoka, Takeuchi, Kuwana.

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Biologic-free remission of established rheumatoid arthritis after discontinuation of abatacept: a prospective, multicentre, observational study in Japan

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Abstract

Objective. The aim of this study was to determine whether biologic-free remission of RA is possible with discontinuation of abatacept.

Methods. Japanese RA patients in 28-joint DAS with CRP (DAS28-CRP) remission (<2.3) after >2 years of abatacept treatment in a phase II study and its long-term extension entered this 52 week, multicentre, non-blinded, prospective, observational study. At enrolment, the patients were offered the option to continue abatacept or not. The primary endpoint was the proportion of patients who remained biologic-free at 52 weeks after discontinuation. Clinical, functional and structural outcomes were compared between those who continued and those who discontinued abatacept.

Results. Of 51 patients enrolled, 34 discontinued and 17 continued abatacept treatment. After 52 weeks, 22 of the 34 patients (64.7%) remained biologic-free. Compared with the continuation group, the discontinuation group had a similar remission rate (41.2% *vs* 64.7%, $P=0.144$) although they had a significantly higher mean DAS28-CRP score at week 52 (2.9 *vs* 2.0, $P=0.012$). The two groups were also similar with regard to mean HAQ Disability Index (HAQ-DI) score (0.6 for both, $P=0.920$), mean change in total Sharp score (ΔTSS; 0.80 *vs* 0.32, $P=0.374$) and proportion of patients in radiographic remission ($\Delta TSS \leqslant 0.5$) at the endpoint (64.3% *vs* 70.6%, $P=0.752$). Those attaining DAS28-CRP <2.3 or <2.7 without abatacept at the endpoint had significantly lower HAQ-DI score and/or CRP at enrolment. Non-serious adverse events occurred in three patients who continued or resumed abatacept.

Conclusion. Biologic-free remission of RA is possible in some patients after attaining clinical remission with abatacept. Lower baseline HAQ-DI or CRP may predict maintenance of remission or low disease activity after discontinuation of abatacept.

Trial registration: UMIN Clinical Trials Registry, http://www.umin.ac.jp/ctr/ (UMIN000004137).

Key words: rheumatoid arthritis, abatacept, biologic-free remission, observational study.

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Introduction

RA is a systemic inflammatory disease characterized by polyarthritis and progressive joint destruction. In RA, synovial monocyte-/macrophage-like cells and dendritic cells serve as antigen-presenting cells (APCs) due to their expression of antigen–MHC class II complexes and co-stimulatory molecules such as CD80 and CD86 [1]. Activated $CD4^+$ T cells expressing CD28 significantly infiltrate into the synovial membrane of affected joints and exacerbate synovitis and joint destruction by secreting inflammatory cytokines and activating synovial cells and osteoclasts [2–4]. The activation of $CD4^+$ T cells is therefore an important stage in the development of rheumatic synovitis, with the CD28-mediated co-stimulatory signal being required for full T cell activation and playing a major role in the immunopathological process of RA.

Abatacept is a genetically engineered humanized fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte-associated molecule 4 (CTLA-4) connected to a modified Fc region (hinge-CH2-CH3 domain) of human immunoglobulin G-1. Abatacept is a novel anti-rheumatic drug that acts by modulating the activation of naive T cells through the competitive binding of co-stimulation molecules expressed on APCs (CD80 and CD86) and blockade of $CD4^+$ T cell co-stimulation via CD28 [5].

Abatacept has been reported to control disease activity, prevent or delay joint destruction and improve quality of life [6–12]. Further, abatacept exhibits similar efficacy in Japanese MTX-intolerant patients with active RA, achieving clinical remission [28-joint DAS with CRP (DAS28-CRP) <2.6] in 24.6% of patients after 24 weeks [7]. Due to the high cost of biologic DMARDs and concerns regarding their long-term safety, the potential for biologic-free remission has been identified as an issue for further investigation [13, 14]. No previous studies have addressed this potential therapeutic application of abatacept despite evidence of its ability to suppress $CD4^+$ T cell activation in autoimmune diseases such as RA.

Thus we conducted the present study in Japanese RA patients who had completed a phase II study of abatacept [7] and its long-term extension in order to determine whether clinical remission attained with the drug was sustained following its discontinuation.

Methods

Before enrolment in this study, written informed consent was obtained from each participating patient according to the Declaration of Helsinki (updated 2008). Prior to the start of the study, the institutional review board of each centre reviewed and approved the study.

Study design and patients

In the previous phase II study [7], 194 Japanese RA patients received double-blind treatment with abatacept or placebo for 24 weeks in addition to prior MTX therapy and 174 of them entered its long-term extension and received open-label abatacept for a mean of 37.7 months (range 3.6–45.1). Those who had completed the phase II study [7] and its long-term extension were eligible for this multicentre, non-blinded, prospective, observational study if they were in clinical remission (DAS28-CRP < 2.3) and not receiving any other biologic therapy at enrolment. Inclusion criteria for the phase II study were age $\geqslant 20$ years; fulfilment of the 1987 ACR criteria for the diagnosis of RA with a functional status of class I, II or III; previous treatment with MTX at 6–8 mg/week for at least 12 weeks and one or more of the following: $\geqslant 10$ swollen joints (66-joint count), $\geqslant 12$ tender joints (68-joint count) or CRP $\geqslant 1.0$ mg/dl.

Procedures

At enrolment, patients were offered the option to continue or discontinue abatacept during the study. Those who discontinued abatacept treatment (discontinuation group) were periodically followed up for disease activity. Those who chose to continue abatacept (continuation group) were treated with the drug every 4 weeks at its approved dosage and received similar follow-up. Abatacept could be restarted at a fixed dose of 10 mg/kg in response to a sign of relapse (DAS28-CRP > 2.7 at two consecutive visits) or at the investigator's discretion. If restarted after an interval of $\leqslant 12$ weeks, administration was every 4 weeks, whereas if started after an interval of >12 weeks, the first two doses were administered every 2 weeks and subsequent doses every 4 weeks.

During the study, dose modifications of non-biologic DMARDs (e.g. MTX) and glucocorticoids were allowed at the investigator's discretion. Concomitant administration of NSAIDs was permitted, but that of biologic agents was not.

Efficacy outcomes

The primary outcome measure of this study was the proportion of patients who remained biologic-free at 52 weeks after discontinuation of abatacept. Secondary and tertiary outcomes were efficacy and safety, respectively.

RA disease activity was assessed in terms of DAS28-CRP and DAS28-ESR at weeks 0, 4, 12, 24, 36 and 52. If a patient resumed abatacept treatment, this assessment was made at the time of resumption as well as after 12 and 24 weeks.

In accordance with DAS28-CRP scores, disease activity was classified as remission (< 2.3), low ($\leqslant 2.3$ to < 2.7), moderate ($\leqslant 2.7$ to < 4.1) or high ($\geqslant 4.1$) [15]. The proportion of patients in each disease activity class at each specified time and the proportion of patients in DAS28-CRP remission (< 2.3) at week 52 were calculated.

Similarly, disease activity was classified by DAS28-ESR as remission (< 2.6), low (LDA; $\leqslant 2.6$ to < 3.2), medium (MDA; $\leqslant 3.2$ to < 5.1) or high (HAD; $\geqslant 5.1$) [15]. To assess disease impact on a patient's level of functional ability, the HAQ Disability Index (HAQ-DI) was determined at weeks 0, 4, 12, 24, 36 and 52.

Radiographic progression of joint destruction was assessed in terms of van der Heijde-modified total Sharp score (mTSS) [16, 17] at weeks 0 and 52 or at the time of withdrawal from the study, where possible. Changes from baseline in TSS (ΔTSS), joint erosion (ΔJE) score and joint space narrowing (ΔJSN) score at week 52 were determined. The proportion of patients with no (ΔTSS $\leqslant$ 0), little (ΔTSS $\leqslant$ 0.5; defined as radiographic remission) and rapid radiographic progression (RRP; ΔTSS $\geqslant$5) [18] was calculated.

Time to abatacept treatment resumption

The mean time to resumption of abatacept treatment was determined in the discontinuation group.

Safety

Patients remaining on abatacept were monitored for adverse events (AEs) throughout the study period. In the discontinuation group, AE monitoring was done only if and after abatacept was resumed following relapse. To investigate the relationship between the immunogenicity of abatacept and its tolerability, the anti-abatacept antibody titre in blood was measured at the time of discontinuation, time of resumption and 24 weeks after resumption of abatacept, if applicable.

Statistical analysis

Missing data were imputed by linear extrapolation (radiographic assessments) or last observation carried forward (LOCF) (other efficacy variables). Continuous metric data were summarized in terms of descriptive statistics and were expressed as the mean (S.D.). Data between the two groups were compared using Wilcoxon's rank sum test (demographic and baseline characteristics, DAS28, HAQ-DI, ΔTSS, ΔJE and ΔJSN) or Fisher's exact test (proportion of patients in DAS28-CRP remission at week 52 and the proportions of patients with ΔTSS $\leqslant$0, $\leqslant$0.5 and $\geqslant$5).

Results

Patient disposition and baseline characteristics

Fifty-one consenting patients were enrolled and chose to either discontinue ($n=34$) or continue ($n=17$) abatacept. Nine of the 34 patients from the discontinuation group restarted abatacept at the investigator's discretion ($n=8$) or due to relapse ($n=1$). Six patients from the discontinuation group (with an additional patient withdrawn after resumption) and two from the continuation group dropped out of the study, leaving a total of 28 and 15 patients, respectively. Nineteen patients from the discontinuation group remained biologic-free at week 52 (Fig. 1). The demographic and baseline characteristics of the 51 patients enrolled are summarized in Table 1. The two groups had comparable baseline characteristics, except for significantly shorter disease duration and significantly less joint damage in terms of JSN and TSS in those who discontinued abatacept at enrolment ($P<0.05$ for all comparisons).

Efficacy outcomes

Of the 34 patients who discontinued abatacept at enrolment, 22 patients from an intention-to-treat (ITT) analysis (64.7%) remained biologic-free after 52 weeks. While the mean DAS28-CRP score remained constant in the continuation group, it gradually increased over time in the discontinuation group, leading to a significant difference between the groups at week 52 (2.9 *vs* 2.0, $P=0.012$).

This was also true when the subgroup of discontinuing patients who remained in the study and never restarted

FIG. 1 Patient disposition

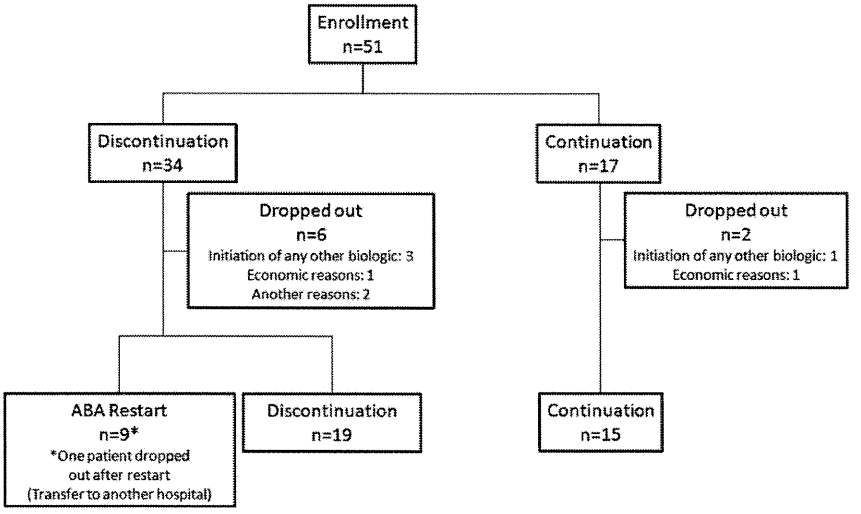


TABLE 1 Patient characteristics

	Discontinuation ($n=34$)	Continuation ($n=17$)	*P*-value
Age, mean (S.D.), years	56.9 (11.4)	60.9 (9.5)	0.195[a]
Male, *n* (%)	5 (14.7)	4 (23.5)	0.443[b]
Female, *n* (%)	29 (85.3)	13 (76.5)	
RA disease duration, mean (S.D.), years	9.6 (5.2)	15.3 (10.5)	0.018[a]
DAS28-CRP, mean (S.D.)	1.8 (0.4)	1.7 (0.5)	0.803[a]
Tender joint count (0–28), mean (S.D.)	0.3 (0.6)	0.1 (0.5)	0.788[a]
Swollen joint count (0–28), mean (S.D.)	0.5 (0.8)	0.6 (0.9)	0.429[a]
HAQ-DI, mean (S.D.)	0.5 (0.5)	0.5 (0.5)	0.356[a]
CRP, mean (S.D.), mg/dl	0.3 (0.5)	0.2 (0.2)	0.285[a]
ESR, mean (S.D.), mm/h	18.7 (9.5)	17.6 (8.5)	0.790[a]
DAS28-ESR, mean (S.D.)	2.4 (0.5)	2.3 (0.6)	0.705[a]
MMP-3, mean (S.D.), ng/ml	79.5 (63.3)[c]	75.3 (46.3)[d]	0.707[a]
RF, mean (S.D.), IU/ml	72.8 (128.5)[c]	50.7 (76.1)[e]	0.822[a]
RF positive, *n* (%)	14 (48.3)[c]	6 (60.0)[e]	0.394[b]
PGA (0–100 mm VAS), mean (S.D.)	12.7 (10.7)	17.4 (15.2)	0.363[a]
Erosion, mean (S.D.)	29.9 (37.9)[f]	62.0 (58.4)	0.015[a]
Joint space narrowing, mean (S.D.)	28.6 (27.2)[f]	55.5 (41.2)	0.020[a]
TSS (0–448), mean (S.D.)	58.5 (64.1)[f]	117.5 (97.7)	0.016[a]
Concomitant use of MTX, *n* (%)	19 (55.9)	12 (70.6)	1.000[a]
MTX dose, mean (S.D.), mg/week	6.7 (2.2)[g]	8.7 (2.3)[h]	0.211[a]
Concomitant use of PSL, *n* (%)	12 (35.3)	8 (47.1)	0.372[a]
PSL dose, mean (S.D.), mg/day	4.0 (2.8)[i]	3.9 (2.8)[j]	0.538[a]

PGA: patient's global assessment of disease activity; VAS: visual analogue scale; RF: rheumatoid factor; TSS: total Sharp score; PSL: prednisolone. [a]Wilcoxon's rank sum test; [b]Fisher's exact test; [c]$n=29$; [d]$n=14$; [e]$n=10$; [f]$n=28$; [g]$n=17$; [h]$n=12$; [i]$n=9$; [j]$n=8$.

abatacept ($n=19$) were compared with the continuing patients remaining in the study ($n=15$; 2.8 *vs* 2.1, $P=0.036$).

Fig. 2 shows the proportion of patients in each RA disease activity class at specified times. In the discontinuation group there was a tendency towards a decrease in the proportion of patients in DAS28-CRP remission and an increase in the proportion of those with HDA as follow-up progressed. At week 52 (LOCF), the proportion of patients in remission was 41.2% in the discontinuation group compared with 64.7% in the continuation group ($P=0.144$). Sixteen of the 17 continuing patients (94.1%) experienced no disease flare (DAS28-CRP <2.7), while 20 of the 34 discontinuing patients (58.8%) were in remission or maintained LDA. Compared with the 14 patients who failed to do so, these 20 patients had significantly lower baseline HAQ-DI scores and CRP ($P=0.036$ and $P=0.048$, respectively). Of the 19 patients who went without abatacept for 52 weeks, 7 were in remission at the endpoint and 12 were not. These two subgroups had comparable baseline characteristics, except that more patients in remission than not in remission at the endpoint were in functional remission (HAQ-DI $\leqslant 0.5$) at enrolment (100% *vs* 41.7%, $P=0.016$). The mean time-averaged DAS28-CRP (TA-DAS28-CRP) [19, 20] was 1.9 (S.D. 0.4) for those who maintained LDA compared with 3.0 (S.D. 0.7) for those who failed to do so ($P<0.0001$).

In contrast to consistently low (<2.6) scores in the continuation group, the mean DAS28-ESR score in the discontinuation group increased slightly, from 2.4 at baseline to 2.7 at week 4, 3.1 at week 12, 3.3 at week 24, 3.5 at week 36 and 3.6 at week 52. According to the endpoint DAS28-ESR scores, 24.2% of the discontinuing *vs* 47.1% of the continuing patients were in remission, 30.3% *vs* 35.3% had LDA, 27.3% *vs* 17.6% had MDA and 18.2% *vs* 0% had HDA. The mean HAQ-DI scores for the two groups followed similar time courses and were 0.6 for both groups at week 52 ($P=0.920$; Fig. 3).

The TSS at weeks 0 and 52 was similar in the discontinuation and continuation groups, but the baseline TSS was higher for the continuation group (Fig. 4A). Mean ΔTSS (0.80 *vs* 0.32, $P=0.374$) and ΔJE (-0.02 *vs* 0.32, $P=0.466$) were similar for the two groups, while mean ΔJSN was significantly greater in the discontinuation group (0.82 *vs* 0, $P=0.035$; Fig. 4B). After correction by linear extrapolation, the proportion of patients in radiographic remission (ΔTSS $\leqslant 0.5$) was 64.3% in the discontinuation group compared with 70.6% in the continuation group ($P=0.752$; Fig. 4C). No radiographic progression was seen in 42.9% and 47.1% of patients, while RRP was seen in 14.3% and 0% of patients in the discontinuation and continuation groups, respectively (Fig. 4C). The four patients who showed RRP after discontinuation had significantly higher CRP at enrolment in this study and lower RF in the previous phase III study compared with the 24 patients who did not show RRP in this group ($P=0.034$ and $P=0.020$, respectively).

FIG. 2 Proportion of disease activity

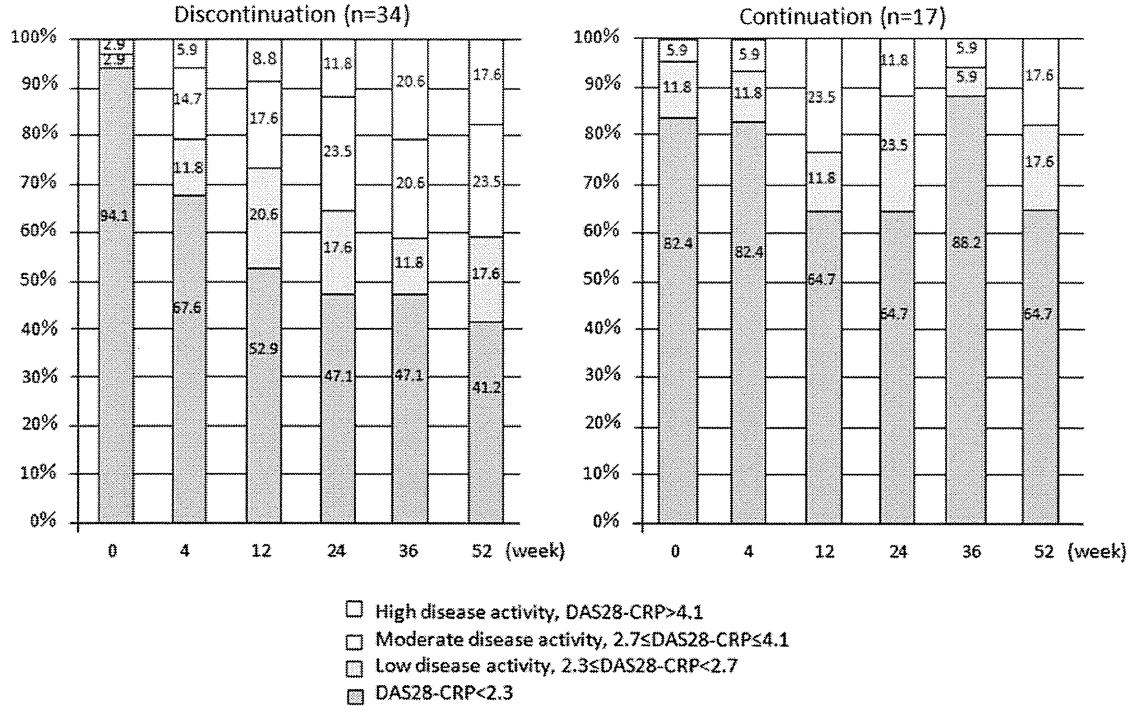
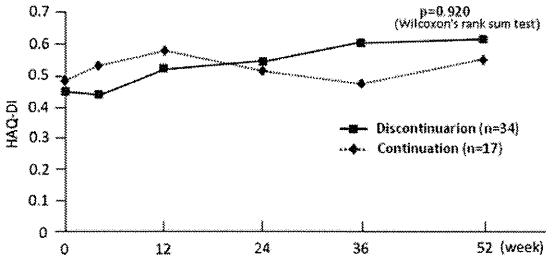


FIG. 3 Transition diagram of HAQ-DI



DI: Disability Index.

In the discontinuation group, 10 of the 14 patients in DAS28-CRP remission at week 52 were evaluable for ΔTSS, of whom 7 (70%) were in radiographic remission. In the continuation group, all 11 patients in DAS28-CRP remission at week 52 were evaluable for ΔTSS and 7 (63.6%) were in radiographic remission.

Resumption of abatacept treatment

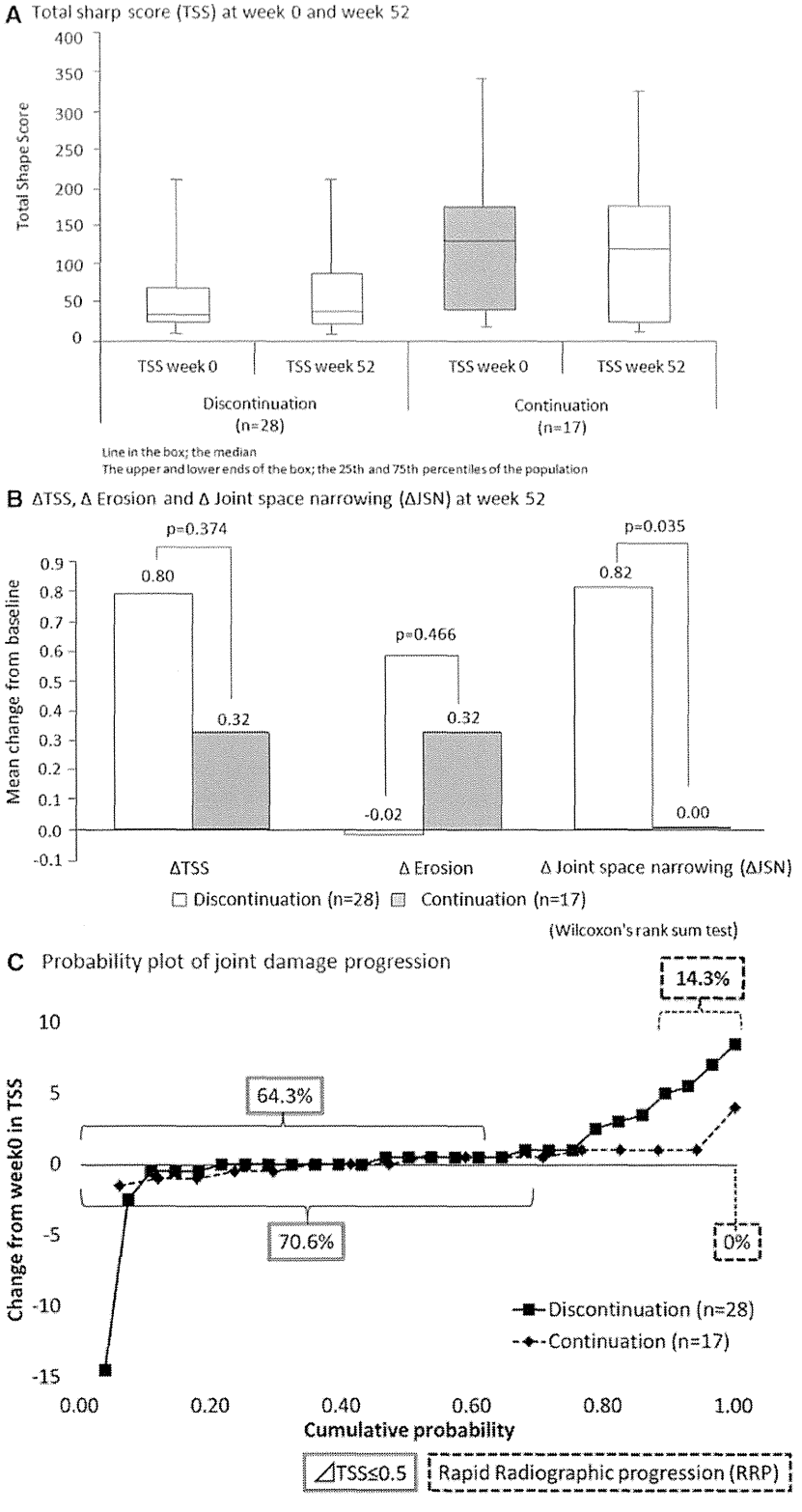
Nine patients resumed abatacept treatment after a mean interval of 149.6 days (S.D. 34.5). After resumption, the mean DAS28-CRP score steadily decreased, from 5.0 (S.D. 1.1) to 3.7 (S.D. 1.6) at 12 weeks and to 3.7 (S.D. 1.7) at 24 weeks, as was observed in the previous phase II/III study [from 4.8 (S.D. 0.8) at baseline to 3.0 (S.D. 0.9) at week 12 and to 2.8 (S.D. 0.9) at week 24; not significant by Wilcoxon's rank sum test].

In the previous study, time to remission in those who resumed ($n = 9$) and did not resume ($n = 25$) abatacept was similar ($P = 0.643$; log rank test); clinical remission was achieved in 2 of 9 (22.2%) *vs* 13 of 25 (52.0%) patients at week 24 and in 88.9% *vs* 96.0% of patients at the endpoint, respectively. The two populations also had comparable demographic and baseline characteristics.

Safety

Non-serious AEs occurred in one patient who resumed abatacept (acute upper respiratory tract infection) and two patients who continued the drug (acute bronchitis in one and low back pain, cystitis, constipation, common cold and left scapulohumeral periarthritis in the second). No serious AEs were reported. Anti-abatacept antibody titre was measured in 26 of the 34 patients upon discontinuation of abatacept, as well as in 7 of 9 and 6 of 9 patients immediately and at 24 weeks after resumption. Positive titres were recorded in four patients (15.4%) upon discontinuation, in two patients (28.6%) immediately after resumption and in no patients at 24 weeks after resumption. Two of the four patients with positive titres upon discontinuation restarted abatacept. Both patients had positive titres again upon resumption, but not after 24 weeks. None of the patients with positive anti-abatacept antibody titre developed AEs or responded poorly to abatacept.

FIG. 4 Total Sharp score



Discussion

Accumulating evidence suggests that $CD4^+$ T cells play a key role in RA-associated inflammation [21–23], although the extent to which they contribute to this disease is not fully understood. Abatacept, which blocks a T cell co-stimulation pathway, has been shown to have favourable efficacy and tolerability profiles in Japanese and non-Japanese MTX-intolerant, TNFinhibitor-intolerant or MTX-naive [early (<2 years)] RA patients [7–12].

The ACR and European League Against Rheumatism treatment recommendations propose that remission or LDA should be the primary target for treatment of RA [24]. Combined therapy with currently available biologic and non-biologic DMARDs can help attain current treatment targets in the majority of RA patients. Nonetheless, the high costs of biologic agents have encouraged ongoing efforts to reduce the economic burden upon patients, including trials to discontinue biologic therapy in patients in sustained clinical remission. While existing data support the potential for biologic-free remission following intensive treatment with TNFinhibitors [25–28], definitive evidence for this potential following discontinuation of abatacept is limited. One study suggested that there was no further radiographic or MRI progression of joint destruction after discontinuation of abatacept in patients with undifferentiated inflammatory arthritis or very early RA [29]. Here we determined the potential of abatacept in promoting biologic-free remission in RA patients already in clinical remission.

At week 52, 64.7% of the patients who discontinued abatacept in an ITT population remained biologic-free (primary endpoint). In a drug-free follow-up of 102 RA patients (mean disease duration 5.9 years) who attained LDA with infliximab [25], 55% of the patients maintained LDA and 39 of the 83 patients (47%) who had achieved remission (DAS28 < 2.6) at enrolment remained in remission for 1 year. In a similar study for adalimumab [28], 14 of 22 patients (64%) maintained LDA (DAS28-CRP < 2.7) without the drug for 1 year. On comparison with these TNF inhibitors, abatacept seems to have a similar potential in the induction of biologic-free remission.

After discontinuation of abatacept, the mean DAS28-CRP score gradually increased and reached a level significantly higher than in the continuation group at week 52. This was also true when the mean endpoint DAS28-CRP score was compared between the 19 patients who went without abatacept and the 15 patients who continued the drug for 52 weeks. In the discontinuation group, the number of patients in DAS28-CRP remission decreased and the number of patients with HDA increased. HAQ-DI and CRP are two baseline parameters that were significantly different between those with ($n = 20$) and without ($n = 14$) LDA at week 52. In addition, HAQ-DI is the only baseline parameter that was significantly different between those in remission ($n = 7$) and those not in remission ($n = 12$) without abatacept at week 52. These findings suggest that the HAQ-DI or CRP immediately before discontinuation of abatacept may predict the probability of subsequent maintenance of remission or LDA. According to TA-DAS28-CRP data, those with LDA at the endpoint maintained LDA throughout the period of follow-up. Comparison between the discontinuation and continuation groups showed similar proportions of patients in clinical remission at week 52 and similar changes in the HAQ-DI over time, indicating that the effects of abatacept on clinical and functional outcomes are durable even after discontinuation.

In RA, joint destruction progresses over time, causing significant disability, which imposes an enormous social burden. Although the recently introduced biologic agents, including abatacept, can prevent or delay joint destruction in a proportion of patients, it is not known if they prevent disease relapse following discontinuation. In the present study, radiographic assessment of joint destruction showed no significant difference between those who discontinued and those who continued abatacept with regard to mean ΔTSS or the percentage of patients with ΔTSS $\leqslant 0$, $\leqslant 0.5$ or $\geqslant 5$. These data confirm that abatacept exerts a sustainable effect in preventing or delaying joint damage and thus keeps patients in radiographic remission even after discontinuation. These radiographic benefits of abatacept appear to be comparable to those of infliximab and adalimumab (in early RA), as evidenced by 67% [25] and 81% [27] of patients with LDA remaining in radiographic remission after discontinuation of those drugs.

As a proportion of RA patients have to suspend their biologic therapy for economic or other reasons, we also assessed the efficacy and safety of re-treatment with abatacept after relapse. Re-treatment with abatacept was effective in controlling disease activity but may be less effective than the initial treatment with abatacept, which was evaluated in the previous phase II study [7].

Abatacept was well tolerated after resumption and during extended use, with only non-serious AEs being reported in three patients. Regarding the immunogenicity of abatacept, two of the limited number of patients assessed were positive for anti-abatacept antibody at the resumption of treatment but were negative after 24 weeks. The disappearance of anti-abatacept antibody after resumption of abatacept treatment may reflect the immunomodulatory effect of the drug.

The present study has several limitations. First, this was an exploratory study about the possibility of biologic-free remission after attaining clinical remission with abatacept. This study had no hypothesis to be tested because no data were available about this possibility with any other biologic DMARDs when we planned this study. Second, this was a small, non-randomized, observational study. Only Japanese RA patients who had completed a phase II study of abatacept [7] and its long-term extension and were in DAS28-CRP remission (<2.3) were enrolled, and for ethical reasons they were offered the option to continue abatacept or not at enrolment. As an expected consequence, the two groups were not well matched at baseline; those who chose to discontinue the drug were at an earlier stage of RA and had less progressive joint damage. Therefore data comparing the two groups

should be interpreted cautiously. Third, we imputed missing data for non-radiographic efficacy variables using LOCF, a less favoured method than multiple imputation. This might introduce uncertainly about the reliability of the disease activity data and compromise their interpretation. Despite these limitations, the results are informative, as they indicate that the clinical remission achieved after abatacept treatment is potentially maintained following discontinuation of the drug in some of the patients, particularly in those who have also achieved a low HAQ-DI score and/or low CRP after the treatment. Given that the decision to continue or discontinue abatacept after attaining clinical remission was made by individual patients and their physicians, this finding will also be helpful for implementing the treat-to-target principle in RA practice.

Rheumatology key messages

- The effects of abatacept on clinical, functional and structural outcomes in RA continue after its discontinuation.
- Biologic-free remission of RA can be maintained after attaining sustained clinical remission with abatacept.
- Lower HAQ DI or CRP may predict maintenance of RA remission or low disease activity after discontinuation of abatacept.

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ORIGINAL ARTICLE

Obstacles to the implementation of the treat-to-target strategy for rheumatoid arthritis in clinical practice in Japan

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Abstract

Objective. To clarify the obstacles preventing the implementation of the treat-to-target (T2T) strategy for rheumatoid arthritis (RA) in clinical practice.

Methods. A total of 301 rheumatologists in Japan completed a questionnaire. In the first section, participants were indirectly questioned on the implementation of basic components of T2T, and in the second section, participants were directly questioned on their level of agreement and application.

Results. Although nearly all participants set treatment targets for the majority of RA patients with moderate to high disease activity, the proportion who set clinical remission as their target was 59%, with only 45% of these using composite measures. The proportion of participants who monitored X-rays and Health Assessment Questionnaires for all their patients was 44% and 14%, respectively. The proportion of participants who did not discuss treatment strategies was 44%, with approximately half of these reasoning that this was due to a proportion of patients having a lack of understanding of the treatment strategy or inability to make decisions. When participants were directly questioned, there was a high level of agreement with the T2T recommendations.

Conclusion. Although there was a high level of agreement with the T2T recommendations, major obstacles preventing its full implementation still remain.

Keywords

Implementation, Obstacle, Rheumatoid arthritis, Treat-to-target

History

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Introduction

Recent insights into rheumatoid arthritis (RA) are leading to a new era in which the pursuit of remission and the prevention of irreversible joint destruction and physical functional impairment is the primary goal of treatment [1,2]. In parallel, there is evidence that treating RA to a target value via composite measures of disease activity results in a significantly improved clinical outcome [3,4]. To help facilitate this future goal the Treat-to-Target (T2T) strategy is an international initiative aimed at proposing global standard procedures in the management of RA. The T2T steering committee has developed 4 overarching principles and 10 recommendations based on clinical evidence through systematic literature review and expert opinion refined from a Delphi-like process [5].

In 2010 an anonymous worldwide survey was conducted on the proposed T2T recommendations for implementation that involved over 1901 rheumatologists. Results showed a very high level of agreement with scores of more than 8.5 for all of the recommendations [6]. However, the study also revealed that in some of the items approximately 10% of participants did not apply the recommendations in clinical practice, and 20–45% of these participants indicated that they would not change this practice [6,7]. In Japan, we have observed similar results of high agreement, but approximately 10% of non-application as a part of the study. Further, a year later, preliminary interviews performed in Japan with 30 rheumatologists and rheumatology nurses suggested that while they agreed with the concept of the T2T recommendations, they were not yet ready to implement them in routine clinical practice. We therefore aimed to identify the obstacles preventing the implementation of the T2T recommendations by rheumatologists at present, with a view to encourage their implementation in the future.

Here, we quantitatively surveyed the current implementation of the T2T recommendations and investigated the obstructions to their implementation.

Subjects and methods

Participants of the survey

Rheumatologists registered on a major website for Japanese physicians were contacted nationwide through e-mail and screened

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to select those who were using the disease activity score (DAS) 28 to evaluate disease activity in RA patients and had started administering biological drugs to more than five RA patients in the previous year. The selected rheumatologists were asked to anonymously complete a web-based questionnaire in November 2011. The sample size was defined in advance as 300, and the survey ended when the number of subjects reached over 300 after a period of 10 days.

Questionnaire

The participants were indirectly questioned about their implementation of basic components of the T2T strategy in a multiple-choice questionnaire. For example, when questioned on the application of Statement 1 ("The primary target for treatment of rheumatoid arthritis should be a state of clinical remission."), the question was not phrased as "Do you apply Statement 1?" In contrast, the participants were first asked "Do you set any 'treatment targets' when treating RA patients with moderate to high disease activity?" Participants were then asked "What are your 'treatment targets' when treating RA patients with moderate to high disease activity? Please choose one or more corresponding answers from the following: 1. Resolution/relief of joint pain, 2. Resolution/relief of joint swelling, 3. Reduction of inflammatory markers (e.g., C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]), 4. Inhibition of progression of joint destruction, 5. Maintenance/improvement of patients' daily life activities, 6. Achievement of low disease activity, 7. Achievement of clinical remission, or 8. Others." Participants who selected "Yes" for the first question and "7. Achievement of clinical remission" for the second were regarded as properly implementing Statement 1. The questionnaire can be viewed in the Supplementary Questionnaire available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.926607. To avoid any bias, we did not disclose the fact that these questions regarded the T2T recommendations until the final section. The questionnaire was developed by T.T. by reference to the preliminary interviews performed with 30 rheumatologists and rheumatology nurses and approved by the other investigators.

In the last section, the participants were directly questioned on their level of agreement with each of the 10 recommendations on a 10-point Likert scale (1 = fully disagree to 10 = fully agree) and the degree to which each recommendation was being applied in clinical practice on a 4-point Likert scale (never, not very often, very often, or always). This methodology was consistent with the international T2T perception survey that was conducted in 2010 [6].

We used descriptive statistics to present proportions of participants pertinent to each issue.

Results

Demographic data of participants

Of the 301 participants, 277 (92.0%) were between 30 and 60 years of age. The number of participants working in each type of health care facility was as follows: university hospitals, 101 (33.6%); general hospitals, 139 (46.2%); and private clinics, 61 (21.3%). The number of participants with a certificate from the Japan College of Rheumatology for each type of membership was as follows: instructor, 92 (30.6%); specialist, 134 (44.5%); and general member, 60 (19.9%). The average number of RA patients seen by each rheumatologist per month was 149.9.

Implementation of treating RA to a primary target of remission using validated composite measures

Of the 301 participants, 228 (75.7%) set treatment targets for nearly all of their RA patients with a moderate to high disease activity, and 72 (23.9%) for a proportion of their RA patients.

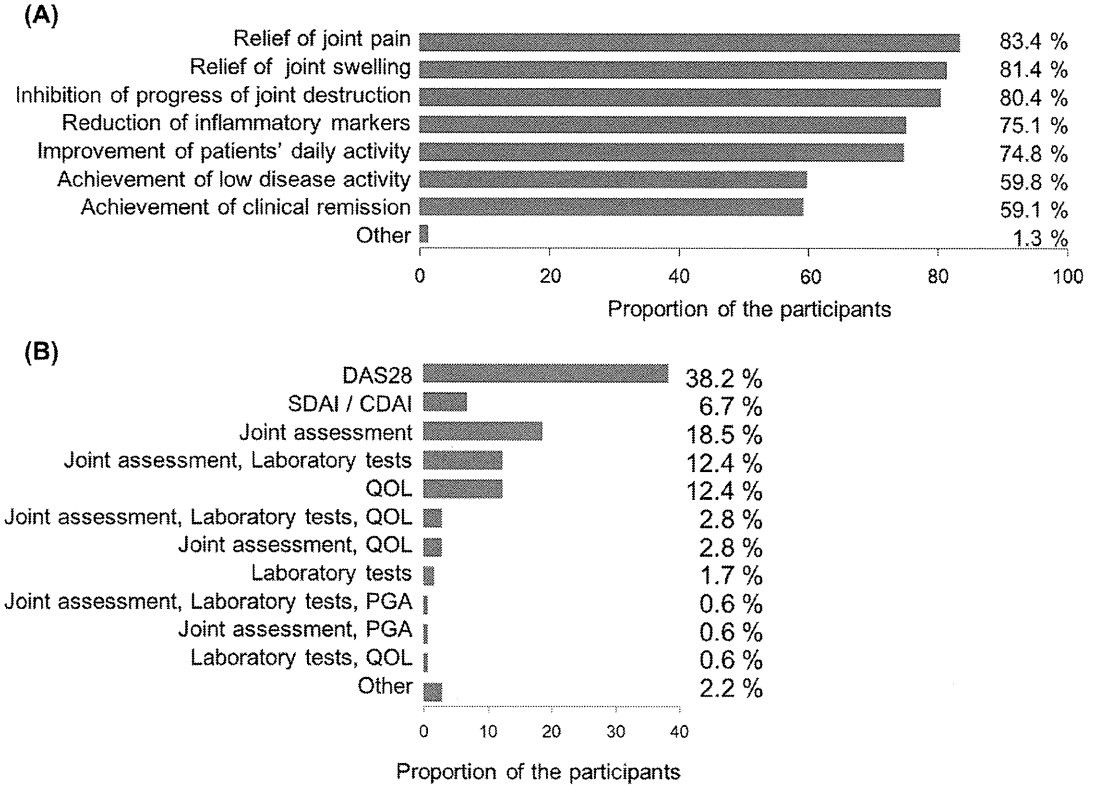

Figure 1. (A) Targets set by rheumatologists in clinical practice. (B) Definitions of clinical remission as treatment targets. The upper two answers included composite measures, and the others included only individual variables. DAS28, disease activity score 28; SDAI, simplified disease activity score; CDAI, clinical disease activity score; Joint, joint assessment; Lab test, laboratory test; PGA, patient global assessment; QOL, quality of life.

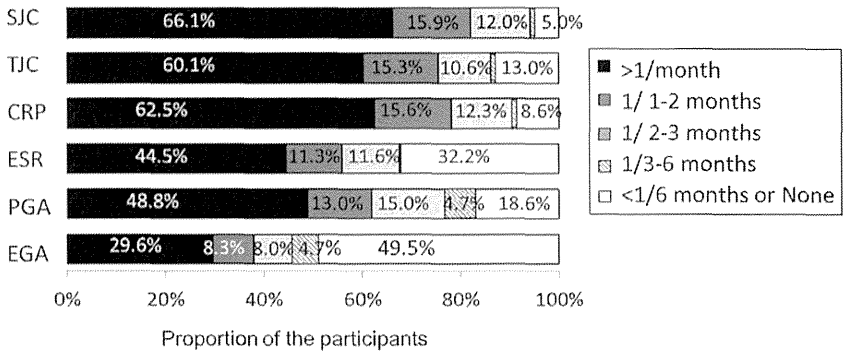

Figure 2. The proportion of rheumatologists who monitored each variable at the indicated intervals. SJC, swollen joint count; TJC, tender joint count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PGA, patient global assessment; EGA, estimator global assessment.

However, only 178 (59.1%) participants set clinical remission as a target (Figure 1A), and of those only 80 (44.9%) used composite measures that included joint assessments (Figure 1B). Of the 301 participants, 26.6% were using remission defined using validated composite measures of disease activity as targets of treatment in routine clinical practice as recommended.

Frequency of disease activity monitoring

The frequencies of monitoring variables pertinent to disease activity in RA patients with moderate to high disease activity are shown in Figure 2. The most frequently monitored variables were swollen joint count (SJC) and tender joint count (TJC), and the least monitored was evaluator global assessment (EGA). The number of participants who monitored each variable at least every month was a follows: SJC, 199 (66.1%); TJC, 181 (60.1%); C-reactive protein, 188 (62.5%); erythrocyte sedimentation rate, 134 (44.5%); patient global assessment, 147 (48.8%); and EGA, 89 (29.6%).

Assessment of structural changes and functional impairment

Regarding the assessment of structural changes 264 participants (87.7%) monitored the X-rays of RA patients with moderate to high disease activity. However, only 177 participants (58.8%) were performing X-ray assessment in more than 80% of their patients (Figure 3). In terms of functional impairment only 131 rheumatologists (43.5%) were routinely monitoring the Health Assessment Questionnaire (HAQ), and this number fell to 67 (22.2%) when limiting to those who performed HAQ assessment in more than 80% of RA patients (Figure 3).

Communication between physicians and patients

When the participants were questioned on communication with patients regarding their treatment strategy and regimen, 131 (43.5%) answered that they did not discuss with all their patients (Figure 4A). Of these participants, 63 (48.1%) answered that this was due to a proportion of patients being unable to understand the treatment strategy and regimen, and 77 (58.8%) that it was due to a proportion being unable to make a decision on the treatment (Figure 4B). When asked whether they calculated DAS28 scores and informed the patients of this during consultations, 176 (58.5%) did not do so at all, and only 64 (20.9%) informed more than 80% of their patients (Figure 4C). One hundred and fourteen (37.9%) participants did not calculate DAS28 during the consultations (i.e., calculate after the patient has left the office or at other available time), with the majority (95, 83.3%) of these citing the lack of time to calculate DAS28 during consultations as a reason (Figure 4D).

Support system for implementation of T2T recommendations

As the implementation of T2T requires joint assessment, calculating composite measures of disease activity, and the education of and communication with RA patients, we investigated the proportion of rheumatologists who conducted these multiple processes in clinical practice. Joint assessment was conducted by 286 (95.0%) participants (Figure 5A). Two hundreds seventy-nine (92.7%) calculated DAS28 themselves while 22 (7.3%) were helped by nurses or other medical staffs (Figure 5B). Although nearly all participants explained the disease, the laboratory tests for RA, and treatment of RA to their patients, only 14.0–15.9% of participants received assistance from other healthcare providers, such as nurses or pharmacists (Figure 5C).

Agreement with and application of T2T recommendations from questions in a direct manner

In the last section of the questionnaire, participants were directly questioned on their level of agreement with the T2T recommendations and the extent to which they applied them in clinical practice. There was a high level of agreement, with each of the 10 recommendations receiving a score of greater than 8.0 (Figure 6A). The highest scores were for Recommendations 1 (9.1) and 9 (9.0), and the lowest for Recommendations 8 (8.0) and 10 (8.1). In terms of application into clinical practice, the

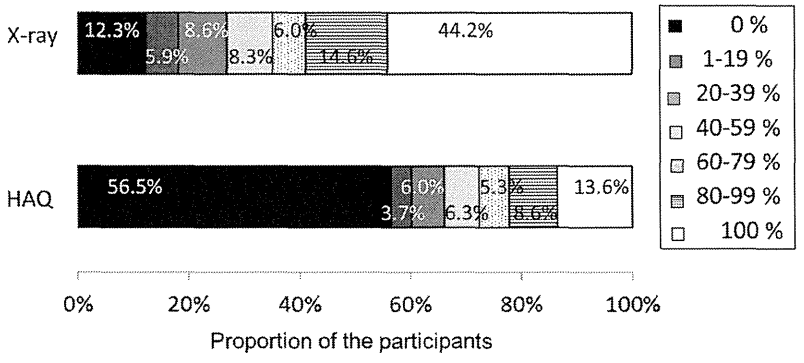

Figure 3. The proportion of rheumatologists who routinely monitored X-rays or Health Assessment Questionnaires (HAQ) for the indicated percentages of RA patients with moderate to high disease activity. HAQ, health assessment questionnaire.

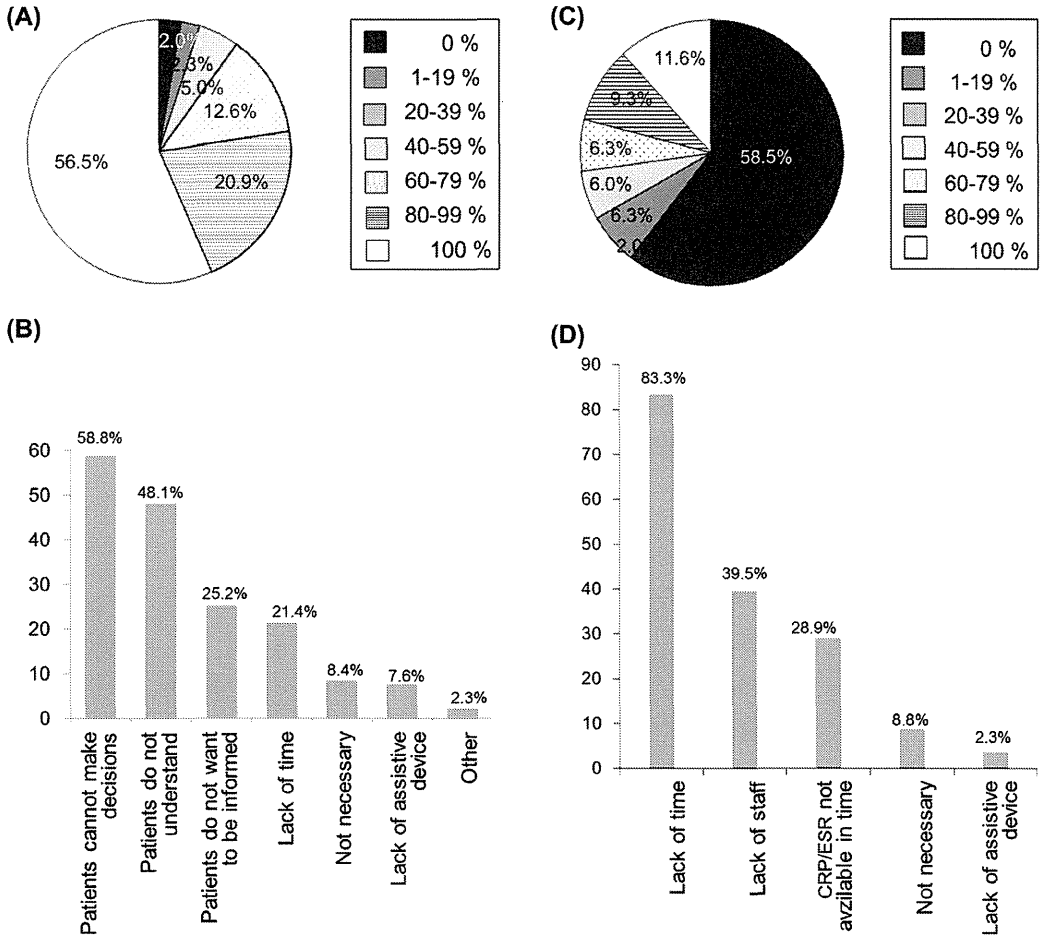

Figure 4. (A) The proportion of RA patients with moderate to high disease activity with whom the rheumatologists were discussing their treatment strategy and (B) the reasons for not discussing with all their patients ($n = 131$). Multiple answers are allowed. (C) The proportion of patients the rheumatologists informed of their DAS28 score during consultations and (D) the reasons for not calculating DAS28 during consultations ($n = 114$). Multiple answers are allowed.

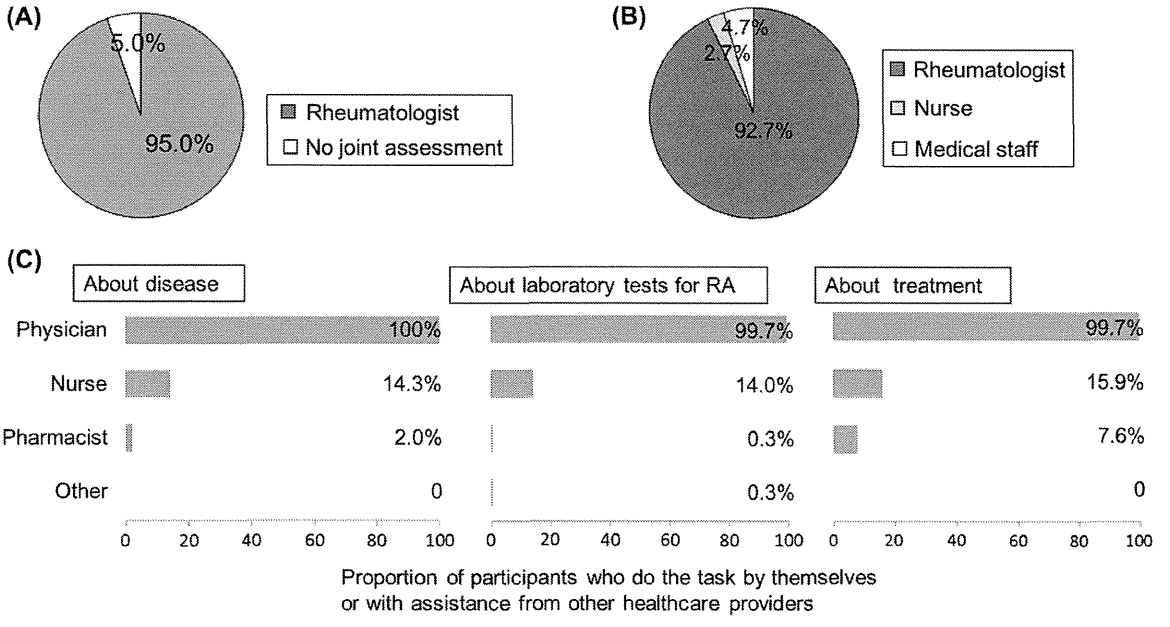

Figure 5. Proportion of participants who (A) assess joints, (B) calculate DAS28 scores, and (C) educate patients with RA in clinical practice by themselves or with assistance from other healthcare providers.

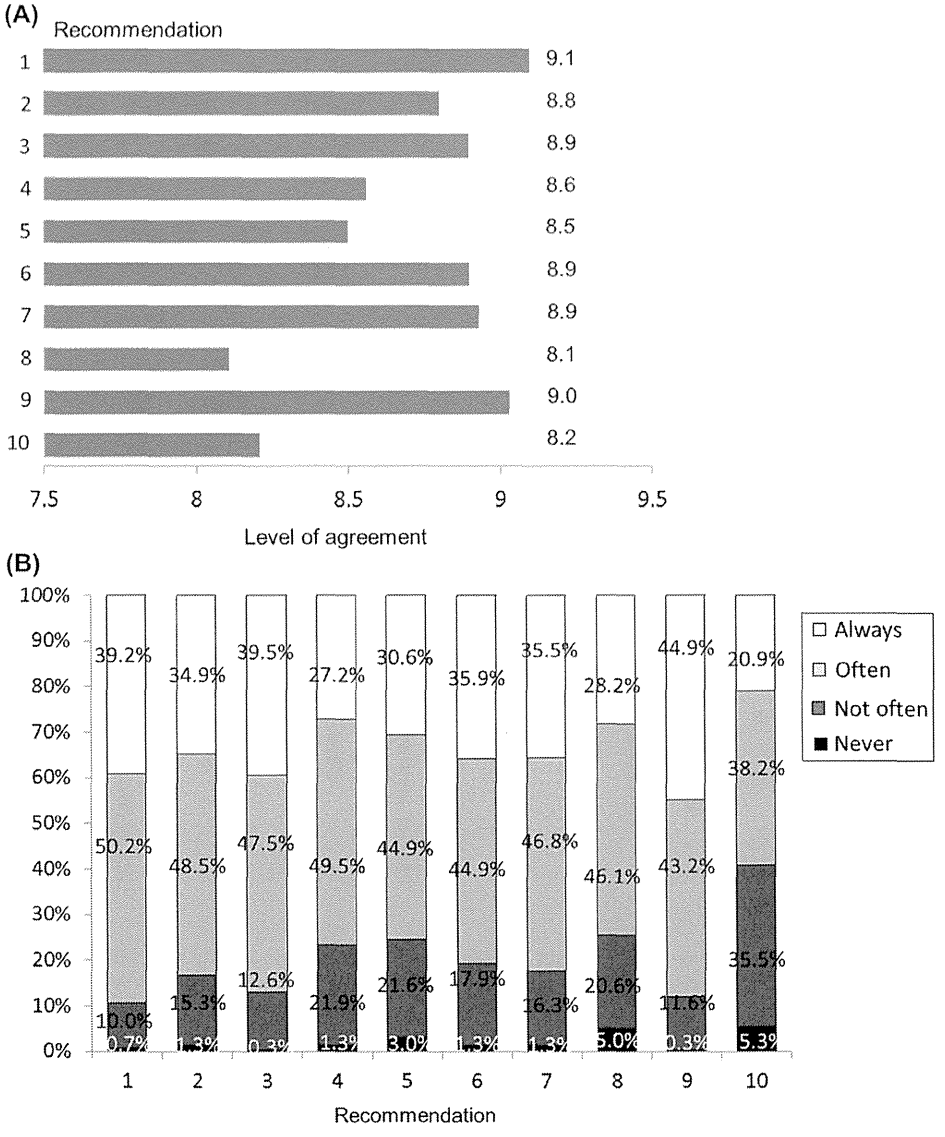

Figure 6. (A) The average level of agreement with and (B) application of the 10 individual T2T recommendations in clinical practice by rheumatologists.

lowest number of responses for "always" and "very often" were for Recommendation 10 (59.1%; Figure 6B). The lowest number of responses for "not very often" and "never" were for Recommendations 1 (10.7%), 3 (12.9%), and 9 (11.9%). There were differences in the results based on indirect questions and those on direct questions on application into clinical practice. The responses for "always" and "very often" regarding Recommendation 1 (clinical remission as a primary target) were 89.4% of participants when directly questioned, which was much higher than the 59.1% when indirectly questioned. A similar trend was observed for Recommendation 7 (consideration of structural damages and functional impairment), that is 82.3% when directly questioned compared to 44.2% (X-ray) or 13.6% (HAQ) when indirectly questioned.

Discussion

Despite the majority of rheumatologists in Japan agreeing with the T2T recommendations for RA, not all implement them properly in clinical practice. This can be attributed to an insufficient understanding of the T2T recommendations by both rheumatologists and patients, a lack of time and support from other healthcare providers during consultations, and patients' passive participation in decision making.

In a similar manner, while the majority rheumatologists agree that they should aim for clinical remission as a primary target of treatment with consideration of structural damages and functional impairment, only 27% of rheumatologists use composite measures appropriately for patients with moderate to high disease activity, and 59% and 22% assess X-ray and HAQ for more than 80% of their patients, respectively. RA cannot be assessed using simple gold standard measures, such as the value of blood pressure when caring for hypertension patients [8], and the complexity of the signs and symptoms requires the application of composite scores [9–11], However, our results show that physicians tend to interpret the individual variables rather than comprehensive composite measures in clinical practice. This might be partly due to physicians not understanding the T2T recommendations well enough to implement them properly, which could be improved by better educating them on the T2T recommendations. This study also revealed the huge burden on rheumatologists of assessing joints, calculating composite measures, and explaining these aspects of RA to patients. In Japan, patients are free to select rheumatologists or hospitals without any reference, and to see one specified doctor on a regular basis (usually every 1–3 months). Consequently, physicians can only allocate a limited consultation period to each patient and have no time to calculate or explain composite measures. This lack of time is one of the major obstacles in

the implementation of T2T recommendations, and new ways to support physicians should therefore be devised.

Another important finding of this study is the insufficient level of communication between rheumatologists and patients. Nearly half of the rheumatologists involved in this survey answered that a proportion of their patients had a lack of understanding or inability to make decisions regarding their treatment. Further, these rates were much higher than the rheumatologists who referred to the lack of time as the reason why they did not discuss the treatment strategy with all their patients. As a shared decision between patients and rheumatologists is one of the overarching principles of T2T recommendations in RA [5] the next step will be to increase the involvement of patients in the decision making process. The T2T committee has recently launched a worldwide T2T CONNECT project, which is intended to encourage better communication with patients by facilitating intrinsic motivation within patients via Motivational Interviewing method [12] and engaging them in treating RA to target. In order to compensate the shortness of time and to have patients develop understandings, innovative tools that are one of critical elements in the T2T CONNECT project are considered to be helpful. Although some tools such as illustrative leaflets and DAS calculators are now available, more tools should be invented. Moreover, to urge more T2T strategies implementation, we rheumatologists should prove substantial evidence of the benefit of T2T strategies in Japanese patients with RA.

We should note the discrepancy between the results based on indirect questionnaires and the answers to direct questions on components in T2T strategy. It is apparent that not all physicians who answered that they apply T2T recommendations into clinical practice implement them appropriately. Conducting a survey by indirectly questioning the components in T2T strategy may therefore provide a more accurate representation of the actual situation in clinical practice.

There are limitations to consider when interpreting the results of this study. First, as this survey was conducted in Japan the circumstances in clinics are therefore hectic, as mentioned above, and these results may not be representative of other counties. For example, a study from the Netherlands that retrospectively surveyed 100 patients with RA participating in a cohort reported a high availability of DAS28 and successful implementation of the T2T recommendations [13]. A multinational survey with a higher number of participants is therefore warranted. Second, the participants who were contacted through e-mail may not necessarily represent the average rheumatologist. However, we believe from participants' demographic data that they are justifiable enough for analysis. Third, some rheumatologists might agree with T2T strategies but use different evaluative criteria rather than DAS28, SDI, CDAI, or HAQ. These issues are different from an insufficient understanding of T2T strategies, and we could not view them exactly through the questionnaire we used.

In conclusion, while the majority of rheumatologists in Japan agree with the T2T recommendations, there is still a room for improvement in implementation in clinical practice by ensuring that rheumatologists have a sufficient understanding, that support systems allow rheumatologists to implement them more easily, and that patients have better understandings on RA and its treatment strategy and take a greater participation in the decision-making process.

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Conflict of interest

YK and HO have no competing interest. TK has received research grants from Abbott (Abbvie), Astellas Pharma Inc., Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma, MSD KK, Pfizer Inc. and Takeda Pharmaceutical Co.Ltd., KY has received research grants from Astellas Pharmaceutical, Chugai Pharmaceutical, Eizai Pharmaceutical, Immunofuture Inc, Mitsubishi Tanabe Pharma Corporation, Santen Pharmaceutical and Wyeth. NM has received research grants from Abbott, Astellas Pharmaceutical, Banyu Pharmaceutical, Chugai Pharmaceutical, Daiichi Sankyo Pharmaceutical, Eizai Pharmaceutical, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical and Teijin Pharmaceutical. MH has received research grants from Abbott, Astellas Pharma, Bristol Myers Squibb, Chugai Pharmaceutical, Eisai Pharmaceutical, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical and UCB Japan. HY has received honorarium for the lecture from AbbVie, Chugai, Daiichi Sankyo, Eisai, Mitsubishi Tanabe, Pfizer, Takeda, Teijin Pharma, and has received research grant from AbbVie, Asahikasei Pharma, Astellasm, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eisai, GlaxoSmithKline, Janssen, Mitsubishi Tanabe, MSD, Nippon Kayaku, Pfizer, Santen,Taishotoyama, Takeda, Teijin Pharma. NI has received research grants from Astellas Pharmaceutical, Chugai Pharmaceutical, Eizai Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Kaken Pharma, Abbott, and Bristol Myers Squibb. YT has received consulting fees, speaking fees, and/or honoraria from Mitsubishi-Tanabe, Eisai, Chugai, Abbott Japan, Astellas, Daiichi-Sankyo, Abbvie, Janssen, Pfizer, Takeda, Astra-Zeneca, Eli Lilly Japan, GlaxoSmithKline, Quintiles, MSD, Asahi-Kasei and has received research grants from Bristol-Myers, Mitsubishi-Tanabe, Abbvie, MSD, Chugai, Astellas, Daiichi-Sankyo. TT has received research grants from Abbott, Astra Zeneca, Bristol Myers Squibb, Chugai Pharmaceutical, Eisai Pharmaceutical, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Novartis, Takeda Pharmaceutical and Wyeth.

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Supplementary material available online

Supplementary Questionnaire.