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EXTENDED REPORT

Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study

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ABSTRACT

Objectives To investigate the possibility of discontinuing adalimumab (ADA) for 1 year without flaring (DAS28-erythrocyte sedimentation rate (ESR) ≥3.2), and to identify factors enabling established patients with rheumatoid arthritis (RA) to remain ADA-free.

Methods Of 197 RA patients treated with ADA +methotrexate (MTX), 75 patients who met the ADA-free criteria (steroid-free and sustained DAS28-ESR remission for 6 months with stable MTX doses) were studied for 1 year.

Results The mean disease duration and DAS28-ESR score in 75 patients was 7.5 years and 5.1 at baseline, respectively. The proportion of patients who sustained DAS28-ESR <2.6 (48%) and DAS28-ESR <3.2 (62%) for 1 year were significantly lower in the ADA discontinuation group than in the ADA continuation group; however, in patients with deep remission (DAS28-ESR ≤1.98) identified by receiver operating characteristics analysis following logistic analysis, these rates increased to 68% and 79%, respectively, with no significant difference between both groups. Remarkably, ADA readministration to patients with flare was effective in returning DAS28-ESR to <3.2 within 6 months in 90% and 9 months in 100% patients; among the patients who sustained DAS28-ESR <3.2 during ADA discontinuation, 100% remained in structural remission and 94% in functional remission.

Conclusions The possibility of remaining ADA-free for 1 year was demonstrated in established patients with RA with outcomes that ADA can be discontinued without flaring in 79% patients with deep remission, with similar rates in the ADA continuation group, and showed no functional or structural damage in patients with DAS28-ESR <3.2. ADA readministration to patients with flare during ADA discontinuation was effective.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease, leading to synovial hypertrophy and adjacent bone and cartilage destruction.[1] Synovial macrophages, fibroblasts and lymphocytes are critical to the pathogenesis of this disease, and it is believed to be partially mediated by overproduction of cytokines, such as tumour necrosis factor-α (TNFα).[2 3] Anti-TNF therapy in combination with methotrexate (MTX) has revolutionised RA treatment, leading to clinical, functional and structural remission; currently, discontinuation of TNF inhibitors without disease flare is our next goal. Because of unresolved risks, such as serious infection[4] and lymphoma[5 6] associated with continuous use of biologics, discontinuation is desirable from the standpoint of risk reduction and cost effectiveness, especially for patients with clinical remission, considering the economic burden associated with this expensive treatment. Thus, studies studying the possibility of biologic-free therapy after clinical remission are important to give a hint to determine whether this is an achievable goal.

Monoclonal antibodies against TNFα, such as infliximab (IFX) and adalimumab (ADA), block the biological functions of TNFα by binding to soluble TNFα and also transmembrane TNFα (mTNFα),[7] which induces complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity[8] and outside-to-inside signalling.[9] These responses exert their pathogenic effect by inducing apoptosis of mTNFα-bearing cells; therefore, biological-free remission is highly expected in some patients under remission by IFX and ADA therapy because their mechanisms of action enable them to eradicate target cells producing inflammatory cytokines in joints of the responsive patients. In fact, evidence of biologic-free status has been reported in studies of TNF20,[10] BeSt,[11] HIT HARD[12] and OPTIMA[13] in early RA and remission induction by Remicade in RA (RRR)[14] in established RA. However, there is no established firm evidence for maintenance of clinical remission, and no standardised characteristics of patients with established RA in whom biologics can be successfully discontinued.

To address this problem, we investigated the potential for discontinuing biologics using ADA, specifically by thoroughly examining the following four questions: (1) whether the 1-year remission rate in the ADA discontinuation group is comparable with that in the ADA continuation group, (2) which factors are related to sustained remission, (3) whether patients with flare can be rescued by readministration of ADA and (4) whether functional and structural remissions are maintained during ADA discontinuation.

METHOD

Patients

Totally, 197 RA patients (age ≥18 years) with active moderate-to-severe RA, according to the 1987

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American College of Rheumatology (ACR) criteria[15] and DAS28- erythrocyte sedimentation rate (ESR) ≥3.2, and who displayed inadequate response to MTX (4–16 mg/w according to the Japanese MTX package insert) and/or had other non-biological disease-modifying antirheumatic drugs (DMARDs) initiated treatment with ADA between July 2008 and April 2011, according to the Japanese package insert and Japan College of Rheumatology (JCR) for anti-TNF drugs.[17 18] Patients received subcutaneous injection of 40 mg ADA combined with MTX every other week. Administration of DMARDs and oral steroids was at the rheumatologists' discretion, but intensive treatment with ADA + MTX was initiated with an aim of remission induction in those patients whenever appropriate. The decision to discontinue ADA was taken on the basis of patients' agreement with the physician's judgment. Patients with flare, defined as DAS28-4ESR ≥3.2, were rescued by readministration of ADA or other treatments, such as increases in the dose of MTX. The treatment decisions taken throughout the study were based on the JCR guidelines and shared decisions between patients and rheumatologists.

Study design

This study was based on the HONOR (humira discontinuation without functional and radiographic damage progression following sustained remission) study, an open-label, non-randomised trial that was approved by the ethics review board of the University of Occupational and Environmental Health, Japan, and registered at the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) as UMIN000006669 to evaluate disease activity, functional disability and radiographic damage progression after discontinuing ADA (ADA-free). The ADA-free criteria were set as follows: maintenance of remission for ≥6 months, assessed by a disease activity score based on erythrocyte sedimentation rate using 28 joints (DAS28-ESR) <2.6[18] without glucocorticoids and non-steroidal anti-inflammatory drugs or coxibs and maintaining a stable MTX dose for at least 12 weeks.[19] Clinical assessment was performed at the initiation of ADA treatment, at discontinuation of ADA and at 6 and 12 months after ADA discontinuation. In this paper, we focused on the outcomes 1 year after ADA discontinuation to address our four key questions regarding biologic-free potential as described in the introduction section. Of the 197 patients who initiated ADA treatment, 75 met the ADA-free criteria by January 2012 and were divided into two groups, ADA discontinuation (n=52) and ADA continuation (n=23), on the basis of patient agreement. Disease activity was assessed using DAS28-ESR and the simplified disease activity index (SDAI). Functional and radiographic effects were examined using the health assessment questionnaire-disability index (HAQ-DI)[20] and van der Heijde-modified total Sharp score (mTSS).[21] The study was conducted in compliance with the Helsinki Declaration.

Statistical analysis

Demographic and baseline characteristics were analysed using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables, as shown in tables 1 and 2. Using the variables with $p<0.1$ for comparing sustained remission and failed remission (table 2), univariate logistic regression analysis was performed to investigate factors related to sustained remission for 6 months or 1 year after ADA discontinuation. Multivariate analyses were conducted using variables with $p<0.2$ in the univariate analysis, as described in table 3. A receiver operating characteristics (ROC) curve analysis was conducted using DAS28-ESR, which was identified using univariate and multivariate analysis to determine the cut-off value at the decision time of ADA discontinuation. Disease activity and functional activity between subgroups were compared using Wilcoxon rank sum tests. Radiographic progression and functional outcomes over time were compared using the Wilcoxon signed rank test. All reported p values are two-sided and not adjusted for multiple testing. Any difference with $p<0.05$ was considered statistically significant. The last observation carried forward was used for imputing missing data (n=12) of clinical or functional values

Table 1 Baseline characteristics of RA patients who fulfilled or did not fulfil the ADA-free criteria (A) and who agreed or refused ADA discontinuation (B)

Measurement Items	(A) Fulfilled Criteria (n=75)	(A) Not Fulfilled (n=122)	(A) p Value	(B) Discontinued ADA (n=52)	(B) Continued ADA (n=23)	(B) p Value
Age	60.2±11.7	61.0±11.4	0.8237	60.0±11.4	60.8±12.6	0.6048
Gender, n (M/F)	16/59	14/108	0.0688	12/40	4/19	0.7623
Disease duration (years)	7.5±10.2	9.6±10.3	0.0119*	7.0±9.9	8.6±10.8	0.8136
TJC28	8.0±6.3	9.1±6.8	0.2176	8.3±6.7	7.3±5.4	0.7208
SJC28	6.3±4.8	7.7±5.6	0.0802	6.5±5.2	5.9±3.9	0.8445
EGA (VAS, mm)	32.4±20.6	40.4±23.7	0.0584	31.9±21.3	34.1±18.6	0.5630
PGA (VAS, mm)	41.3±24.2	54.9±24.8	0.0004**	39.4±24.0	45.6±24.7	0.3637
HAQ	0.96±0.65	1.42±0.78	<0.0001**	0.94±0.67	1.01±0.62	0.5450
CRP (mg/dL)	2.10±3.23	3.12±4.35	0.1299	2.27±3.68	1.73±1.86	0.6833
ESR (mm/h)	44.1±32.2	53.0±32.9	0.0374*	43.8±33.4	44.8±30.1	0.8182
RF (U/mL)	152.1±299.9	116.2±164.9	0.5924	112.5±144.4	241.7±492.1	0.1864
MMP-3 (mg/mL)	235±305	321±386	0.2274	225±344	258±197	0.0312***
DAS28-4ESR	5.1±1.3	5.7±1.2	0.0050*	5.1±1.3	5.1±1.4	0.8813
MTX (mg/w)	9.3±2.6	8.6±3.3	0.2736	8.9±2.7	10.2±2.1	0.0317***

Data are reported as means±SD, unless otherwise indicated. Statistical significance was assessed by Fisher's exact test for categorical data and the Wilcoxon rank sum test for continuous data. *p <0.05, **p<0.01: Fulfilled criteria versus Not fulfilled. ***p<0.05: ADA discontinuation versus ADA continuation.
ADA, adalimumab; CRP, C-reactive protein; DAS28, disease activity score 28; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PGA, patient global assessment; MMP-3, matrix metalloproteinase-3MTX, methotrexate; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

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Table 2 Characteristics of patients who sustained or did not sustain remission for 1 year after fulfilling the ADA-free criteria

Measurement items	Sustained remission (n=25)	Failed remission (n=27)	p Value
Age (years)	57.1±13.2	62.6±8.9	0.0833
Disease duration (years)	6.6±8.4	9.8±11.1	0.0488*
ADA admin periods (weeks)	59.8±23.7	75.6±30.0	0.0264*
ESR (mm/h)	11.2±6.3	20.2±11.4	0.0019**
CRP (mg/dL)	0.09±0.15	0.11±0.22	0.3289
DAS28-4ESR	1.7±0.5	2.2±0.4	0.0010**
CDAI	0.9±1.0	1.1±1.6	0.7961
SDAI	1.0±1.0	1.2±1.6	0.6144
HAQ	0.18±0.26	0.26±0.35	0.3531
RF (U/mL)	58.6±67.3	30.9±34.7	0.2096
MMP-3 (mg/mL)	56.0±25.0	49.3±31.4	0.1129
MTX (mg/w)	8.1±2.5	8.6±2.0	0.7645
mTSS	−0.6±1.5	−0.9±2.0	0.5691

Data are reported as means± SD, unless otherwise indicated. Statistical significance was assessed by the Wilcoxon rank sum test. *p<0.05, **p<0.01: sustained remission versus failed remission.
ADA administration periods, adalimumab administration periods; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MMP-3, matrix metalloproteinase-3; MTX, methotrexate; mTSS, modified total sharp score; RF, rheumatoid factor; SDAI, simplified disease activity index.

after the initiation of ADA discontinuation. Linear extrapolation was used to determine ΔmTSS at 1 year, when patients' condition was exacerbated. All analyses were performed using Statview for Windows V.5.0 (SAS Institute, Cary, North Carolina, USA) or Prism 5.0d (Graph Pad Software, San Diego, California, USA).

RESULTS

Patient disposition and characteristics

Totally, 197 patients with RA were treated with ADA from July 2008 to April 2011; their mean DAS28-ESR score was 5.4, mean disease duration was 8.9 years and mean age was 60.7 years at baseline. The proportions of bio-naive patients, and the concomitant use of MTX were 75.6% and 95.4%, respectively (see online supplementary table S1). Of the 197 patients, 75 (38%) fulfilled the ADA-free criteria (steroid-free and sustained DAS28-ESR <2.6 for 6 months with stable MTX doses) by January 2012. The patients who met the criteria had shorter disease duration (7.5 vs 9.6 years, p=0.00119), lower levels of patient global assessment (PGA) (41.3 vs 54.9 mm, p=0.0004), HAQ-DI score (0.96 vs 1.42, p<0.0001), ESR (44.1 vs 53.0 mm/h, p=0.0374) and DAS28-4ESR (5.11 vs 5.70, p=0.005) than those who did not meet the criteria.

Table 3 Prognostic factor analysis for sustaining remission

Items	Odds	95% CI	χ^2	p Value
(A) Univariate logistic regression analysis				
Age (years)	0.955	0.907 to 1.007	2.942	0.0863
Duration, disease (years)	0.964	0.908 to 1.025	1.379	0.2403
ADA admin periods (weeks)	0.978	0.956 to 1.000	3.82	0.0507
DAS28-4ESR	0.094	0.020 to 0.438	9.07	0.0026**
RF (U/mL)	1.011	0.998 to 1.025	2.884	0.0895
(B) Multivariate logistic regression analysis				
Age (years)	0.963	0.963 to 0.906	1.441	0.2300
ADA admin periods (weeks)	0.985	0.985 to 0.959	1.254	0.2629
DAS28-4ESR	0.143	0.143 to 0.029	5.653	0.0174**
RF (U/mL)	1.012	1.012 to 0.996	2.127	0.1448

Univariate logistic regression analysis was performed using items with p<0.1 in table 2 to investigate factors related to sustained remission for 1 year after ADA discontinuation. Then, multivariate analyses were conducted using the variables with p<0.2 in the univariate analysis. Using the DAS28-4ESR values which were significant in logistic analysis, ROC analysis was conducted with the response (dependent) variable of if DAS28-4ESR <2.6 (1) or ≥2.6 (0) 1 year after discontinuation of ADA and the explanatory variable of DAS28-4ESR at the timing of ADA discontinuation.
**p<0.01: Wald test.
ADA administration periods, adalimumab administration periods; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

Background comparison between ADA continuation and discontinuation

Of the 75 patients who met the ADA-free criteria, 52 (69%) agreed to ADA discontinuation (table 1B). When the patients' backgrounds were compared between those who agreed and those who disagreed, matrix metalloproteinase (MMP)-3 (225 vs 258 mg/mL, p=0.0312) and mean dose of MTX (8.9 vs 10.2 mg/w, p=0.0317) were significantly lower in the ADA discontinuation group than the ADA continuation group.

Clinical disease activity

Comparison between ADA continuation and discontinuation

The DAS28-ESR remission rate (83%) in the ADA continuation group was significantly higher (48%) than that in the ADA discontinuation group 1 year after the continuation or discontinuation decision was made (p=0.0056; figure 1A). However, when SDAI was used for evaluation, there was no marked difference in the remission rates (≤3.3) between the ADA continuation and discontinuation groups, as shown by their values of 70% and 60%, respectively (p=0.4502). Similar outcomes were observed in the rates of low disease activity (LDA), that is, there was a significant difference in the evaluation using DAS28 (91% in ADA continuation, 62% in ADA discontinuation, p=0.0122), but there was no significant difference in the evaluation using SDAI (≤11.0) between the groups (96% in ADA continuation, 77% in ADA discontinuation, p=0.5690). Although all the proportions were higher in the ADA continuation group, at least 60% of the ADA discontinuation group showed LDA on DAS28-ESR and SDAI evaluations.

Effects of ADA readministration

During the ADA-free period, approximately 40% patients experienced flare (DAS28-ESR ≥3.2; figure 1B). Although MTX dose was escalated to rescue the failure, it was not effective in most patients (75%); furthermore, reinitiating ADA with or without MTX dose escalation resulted in the reinduction of LDA by 90% within 6 months and by 100% within 9 months. ADA restart due to a relapse was not associated with any harmful effects.

Possibility of becoming ADA-free

Characteristics of patients with sustained remission

When patient backgrounds were compared between those who experienced sustained (n=25) and unsustained (n=27) DAS28-ESR remission for 1 year, a statistically significant difference was observed in four items: (1) RA disease periods (p=0.0488), (2) ADA treatment periods (p=0.0264), (3) ESR value (p=0.0019) and (4) DAS28-ESR score (p=0.001; table 2).

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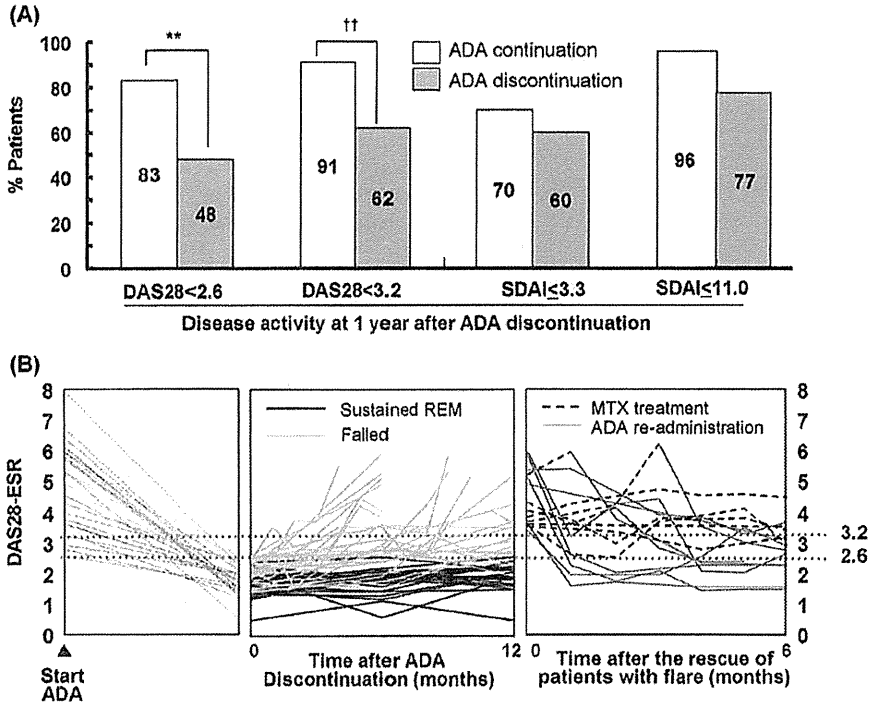

Figure 1 Clinical outcomes evaluated by DAS28- erythrocyte sedimentation rate (ESR) or simplified disease activity index (SDAI) after ADA discontinuation and effects of ADA readministration to patients with flare. (A) shows the proportion of patients with sustained remission and low disease activity (LDA) evaluated using DAS28-ESR (DAS28) or SDAI. Each rate at 1 year after ADA discontinuation was compared with that in the ADA continuation group (Fisher's exact test). (B) shows the time course of changes in DAS28 including rescues of patients with flare (Left: ADA initiation to discontinuation, Middle: ADA discontinuation to 1 year later, Right: Flare to 6 months following rescue with methotrexate (MTX) or ADA). **p<0.01: ADA discontinuation versus ADA continuation using DAS28. In the comparison using SDAI, no significant difference was observed (p=0.4502 for remission, p=0.5690 for under LDA).

Factors affecting sustaining remission

In the analysis of predictive factors related to sustaining remission for 1 year, only DAS28-ESR had a marked correlation with sustained remission in univariate and multivariate analyses (table 3). Subsequent ROC analysis for high estimation of sustained remission indicated a lower cut-off value for the biologic-free remission of 1.98 than the threshold for DAS28-ESR remission of 2.6. This value was similar to 2.16, which was calculated using the data to estimate sustaining remission for 6 months with the sensitivity 90%, specificity 68.2% and AUC 0.86, indicating that deep remission before discontinuing ADA would be a key in established patients with RA.

ADA continuation versus discontinuation in patients with deep remission

Disease activity in patients with deep remission (DAS28-ESR ≤1.98) was investigated 1 year after ADA discontinuation (figure 2A). In the ADA discontinuation group, 79% and 89% patients had values of DAS28-ERS <3.2 and SDAI ≤11.0, respectively, and their remission rates were approximately 70% in both cases (DAS28-ESR <2.6: 68%, SDAI ≤3.3: 75%). Comparison of the data in patients with deep remission with those of the ADA continuation group revealed no significant difference (p=0.2282–0.7067).

Comparison between mild and deep remission

The prognosis 1 year after discontinuing ADA was compared between patients with mild (1.98 < DAS28-ESR<2.6) and deep (DAS28-ESR ≤1.98) remission (figure 2B). As shown in figure 2A, approximately 80% patients with deep remission were able to sustain LDA, whereas, only 42% patients with mild remission were able to do so, suggesting that mild remission may be insufficient for ADA discontinuation in established RA.

Influence of ADA discontinuation on structural and functional remission

In patients with LDA (DAS28-ESR <3.2) 1 year after ADA discontinuation (n=31), the mean HAQ-DI (0.15) and functional remission (HAQ-DI ≤0.5) rate (94%) were similar to those 1 year earlier (figure 3). The structural remission rate was 100% (mTSS <0.5), demonstrating that maintaining LDA makes it possible to sustain functional and structural remission for at least 1 year after becoming ADA-free. In patients with flare (DAS28-ESR ≥3.2) during the year after ADA discontinuation (n=21), the mean HAQ-DI and mTSS significantly increased from 0.30 to 0.57 (p=0.0018) and −0.74 to 0.85 (p=0.0431), respectively, and the functional and structural remission rates decreased from 76% to 57% and from 100% to 83%, respectively. In the ADA continuation group, 21 patients sustained LDA during the year, but there were only two patients with flare; thus statistical comparison was not performed for the patients with flare. In the patients with sustained LDA, there were no statistically significant differences in HAQ (p=0.1579) and ΔmTSS (p=0.6422) between the ADA continuation and discontinuation groups (see online supplementary figure S1).

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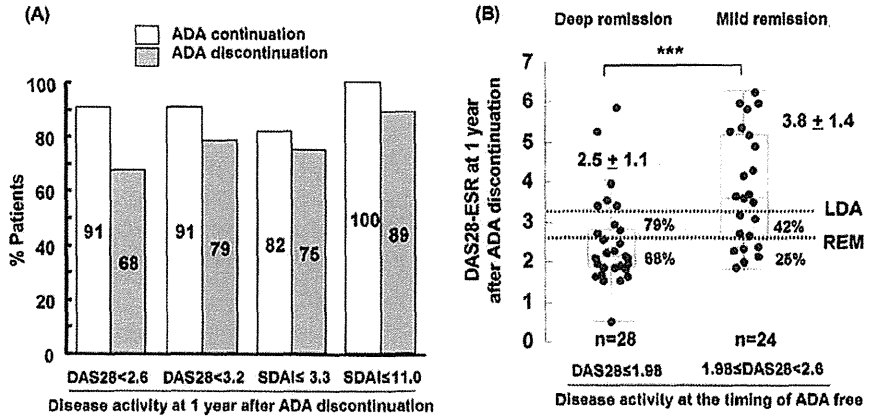

Figure 2 Clinical outcomes in patients with deep remission and influence of the degree of remission. The percentages of patients in remission or with low disease activity (LDA) at 1 year after fulfilling the ADA-free criteria were investigated in patients with deep remission and compared between the ADA discontinuation and continuation groups, using a cut-off value of DAS28-4 erythrocyte sedimentation rate (ESR) ≤1.98 identified using receiver operating characteristics (ROC) analysis. No significant differences were observed between the groups (p=0.228 for DAS28-ESR<2.6, p=0.649 for DAS28-4ESR<3.2, p=0.707 for simplified disease activity index (SDAI) ≤3.3, p=0.545 for SDAI≤11; Fisher's exact test). (B) shows disease activity at 1 year after ADA discontinuation according to the difference in the degree of remission (deep or mild) when ADA was discontinued. ***p<0.001: deep (DAS28 ≤1.98) versus mild (1.98<DAS28<2.6) remission (Wilcoxon rank sum test).

DISCUSSION

The design of the HONOR study has several characteristics that make it unique and important in the quest for the possibility of biologic-free therapy in established RA by addressing four questions as described in the introduction. The study will follow patients throughout the extended treatment period, and here we evaluated the 1-year data of ADA with the concept of a biologic 'treatment holiday.' Of 197 patients who received ADA + MTX/DMARDs, 75 patients (38%) met the ADA-free criteria (maintenance of remission status for 6 months at least) and the

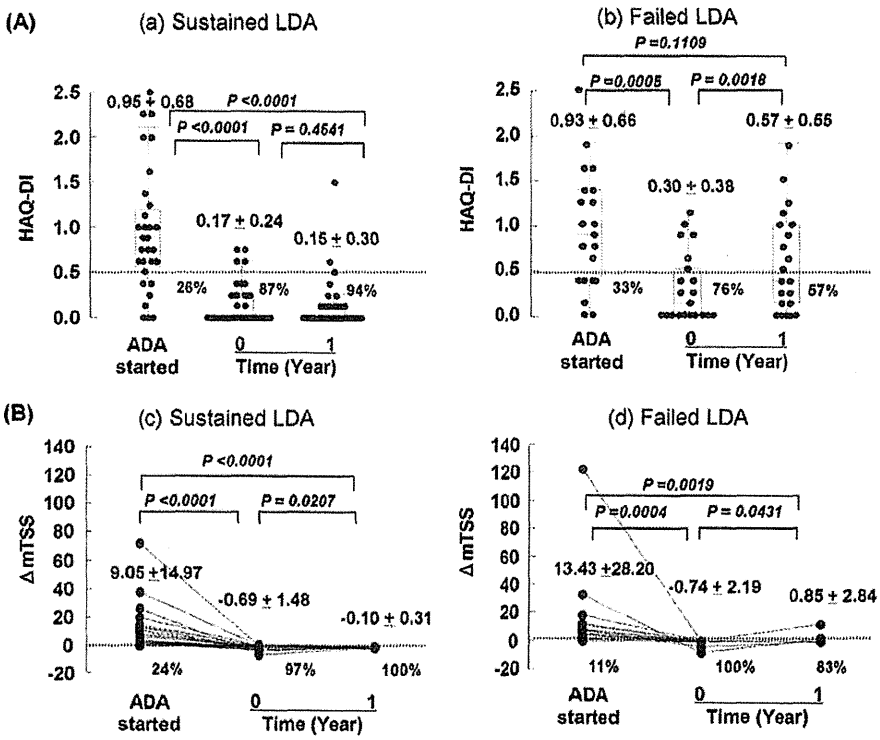

Figure 3 Functional and structural remission in patients with sustained or failed low disease activity (LDA). (A) and (B) show values of health assessment questionnaire-disability index (HAQ-DI) and ΔmTSS in patients with sustained LDA (n=31) at 1 year after ADA discontinuation or failed LDA (n=21) when evaluated by DAS28-4 erythrocyte sedimentation rate (ESR). The percentages show the proportion of patients with sustained functional remission (HAQ<0.5) and structural remission (ΔmTSS<0.5). p Values by Kruskal–Wallis test; mTSS, modified total sharp score.

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majority of the patients who once attained DAS28-ESR remission could maintain stable remission with ADA+MTX/DMARDs under steroid-free conditions. This finding was also supported by the results of a retrospective HARMONY study in Japanese patients treated with ADA.[22] Of the 52 patients who agreed to ADA discontinuation, 25 (48%) sustained DAS28-ESR remission for 1 year. Evaluation using SDAI revealed a remission (≤3.3) rate of 60%, which was similar to the percentage of patients with LDA (62%) evaluated using DAS28, despite our understandings that SDAI has more stringent criteria. As shown in table 2, a marked difference in ESR was observed between patients with and without sustained DAS28 remission. It is well known that ESR level is influenced by many factors, such as infection, or other autoimmune diseases. We also calculated the remission rate using the Boolean approach as a reference (Boolean definition: number of swollen and tender joints each ≤1, C-reactive protein (CRP) ≤1 mg/dL and PGA ≤1); the remission rate was 50%, which was 10% lower than the SDAI remission rate (see online supplementary figure S2). The reason for this was that PGA was >1, probably due to damaged HAQ in established RA because tender and swollen joint counts were 0 in the patients (n=5) who did not meet Boolean remission within those who met SDAI remission. Therefore, the remission rate using SDAI (60%) seems to be more accurate than that obtained using DAS28 (48%), considering that all patients who sustained DAS28 <3.2 (62%) showed 100% structural remission 1 year after ADA discontinuation.

Although the evaluation using DAS28-ESR revealed statistically significant better outcomes in the ADA continuation group than the ADA discontinuation group, evaluation using SDAI or assessing prevention of radiographic damage in patients with LDA by DAS28 revealed no difference between the groups. Consequently, it would not be an overstatement to say that patient outcomes 1 year after ADA discontinuation were the same as those in some patients of the ADA continuation group. In fact, there was no statistically significant difference between the two groups regarding patients with deep remission (DAS28-4ESR ≤1.98), which we identified as a factor necessary for successful ADA discontinuation. Meanwhile, 60% patients with mild remission (1.98≤DAS28-4ESR < 2.6) experienced flaring within a year, suggesting that ADA should be continued in such patients even under DAS28 remission. However, there is a risk that some patients discontinue ADA because of no pain or economic burden, both of which are experienced in daily clinical practice. The good news was that ADA readministration to all patients with flare during ADA discontinuation was effective without harmful effects.

This study had some limitations. This was an open-label, non-randomised study with a limited number of subjects who were divided into two groups partly based on patients' consent, which could have introduced a selection bias. Nonetheless, the study design allowed a comparison between ADA discontinuation approaches (unknown outcomes after ADA discontinuation, expectation of biologic-free disease control in established RA, economical matters, etc) and ADA continuation approaches in routine clinical settings in an ethical manner, with shared decisions between patients and rheumatologists. Confidence in the outcomes would most likely be supported by the results of the RRR and OPTIMA studies that examined biologic-free potential. In the RRR study[14] with long-standing patients with RA, DAS28 ≤2.22 was identified by logistic regression and ROC analysis as a necessary condition for a biologic-free remission, and demonstrated that 71.4% patients with deep remission (DAS28 ≤2.22) were able to continue DAS28 <3.2 for 1 year, whereas only 32.6% patients with 2.22 < DAS28 < 3.2 were able to continue. These results suggest that patients in deep remission (DAS28 of approximately 2.0) have a possibility to achieve biologic-free remission. In the OPTIMA study with early RA,[13] a multinational, double-blind randomised controlled study, with results similar to those of our study were obtained for comparisons between ADA continuation and discontinuation groups. The remission (86%) and LDA (91%) rates in the ADA continuation group in the OPTIMA study were significantly higher than the remission (66%) and LDA (81%) rates in the ADA discontinuation group when compared using the DAS28-CRP criteria, but there was no statistical difference between ADA continuation and discontinuation (remission: 62% vs 51%, LDA: 92% vs 84%, respectively) groups when SDAI criteria were used, and functional and structural outcomes were comparable between the groups. Thus, despite some limitations, the results of the present study are supported by those of the RRR and OPTIMA studies. Additionally, the results of this study demonstrate the potential of remaining ADA-free in established patients with RA, and provide valuable insights into the paradigms of RA treatment in routine clinical settings, considering safety and economical aspects.

Taken together, these results demonstrate that among the patients who met the ADA-free criteria, 48% were able to sustain DAS28-ESR remission after discontinuing ADA, and 60% were in SDAI remission or showed LDA in DAS28-ESR 1 year after becoming ADA-free while maintaining functional and joint structural remission; furthermore, regarding patients with deep remission, disease activity in the ADA discontinuation group was comparable to that in the ADA continuation group, whereas for patients with flare, readministration of ADA was effective. These data indicate that ADA 'treatment holiday' is now feasible in established patients with RA with long-term remission, no steroids and deep remission.

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Contributors YT contributed to study design, overall review, making the manuscript, and the others were involved in performance of the study and review of the manuscript. SH, KS, YT participated in its design and coordination. All authors, except FS, enrolled and managed the patients in clinic. SH, SK, SF participated in radiographic evaluation. SH performed the statistical analysis, and FS helped to draft the manuscript and contributed to reviewers' responses. All authors read and approved the final manuscript.

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Sonographic synovial vascularity of synovitis in rheumatoid arthritis

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Abstract

RA is a condition of multiple synovitis. Abnormal synovial vascularity (SV) is evident with the onset of joint inflammation. The idea of estimating the level of joint inflammation by sonographic SV was conceived with the advancement of US. The ideal treatment strategy, called treat to target (T2T), requires early diagnosis and assessment of RA. Detection of positive SV can be useful for proving the presence of synovitis and finally diagnosing RA. In the assessment of RA, US-based global scores aimed at assessing overall disease activity have the potential to be useful for the achievement of T2T because US can directly detect changes in synovitis. Remaining SV in local joints increases the risk of structural deterioration. RA requires both improvement of overall disease activity and the disappearance of local SV for remission. The evaluation of SV provides various information and contributes to the clinical treatment of RA.

Key words: rheumatoid arthritis, ultrasound, power Doppler sonography, synovitis, synovial vascularity, treat to target.

REVIEW

Introduction

Today, why are rheumatologists enthusiastic to evaluate synovial vascularity (SV) in patients with RA in daily practice? RA is a condition of multiple cryptogenic synovitis characterized by expansion of soft tissue and destructive bone invasion at various joint sites that results in systemic musculoskeletal dysfunction. The pathogenesis of rheumatoid synovitis has been strongly associated with SV (Fig. 1).

Pathological explorations have tried to discover the characteristic pathogenesis of rheumatoid synovitis, and in recent years it has become apparent that with the onset of inflammation, abnormal vascularization is evident in the synovium due to vasodilation or angiogenesis [1–5]. A close relation between SV and synovitis has been confirmed. Presently SV is one of the hottest topics in rheumatology clinics.

Various factors such as the variety of afflicted joint sites or the diversity of disease progression may affect evaluation of the disease activity of RA. Composite scoring, which comprises clinical findings such as tender or swollen joint counts, has been established to evaluate the overall disease activity of RA. Clinical composite scores such as the 28-joint DAS (DAS28), the Simplified Disease Activity Index and the Clinical Disease Activity Index have been proven to be useful by various clinical trials [6, 7]. Although these clinical composite scores assess overall disease activity, they do not satisfactorily alert the clinician to changes in local joints due to their dichotomous judgment for each joint. To achieve deep remission of RA and to halt all abnormal joint destruction, the focus must be on detecting changes in local joint inflammation.

Progress in digital technology has resulted in US systems that produce high-quality images that enable observation of small joints. The novel idea of estimating the level of joint inflammation by sonographic SV was conceived with advancements in power Doppler US (PDS). Newman *et al.* [8, 9] first reported the use of PDS to detect abnormal SV, and Szkudlarek *et al.* [10] compared PDS with dynamic MRI to assess synovitis in finger joints and showed equivalency with both techniques.

With advancements in treatments for RA, early diagnosis and treatment have come to the forefront [11–14]. In response to this, new ACR/ European League Against Rheumatism (EULAR) classification criteria were introduced in 2010 [15, 16]. These criteria specify that patients with probable synovitis are first screened according to

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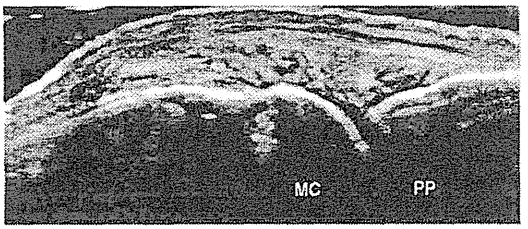
FIG. 1 Longitudinal US image of a metacarpophalangeal joint in a patient with RA.



The multicolour fusion image of grey-scale and corresponding power Doppler images shows inflamed hypertrophic synovial tissue digitally stained in blue and abnormal SV stained in red. MC: metacarpal head; PP: proximal phalanx.

clinical findings. SV reflects the presence of synovitis in the early stage with high specificity.

Here we review the potential of SV detected by PDS for use in the diagnosis and assessment of RA.

Assessment of SV

PDS is essentially a flexible and sonographer-dependent examination. Although PDS is useful for the assessment of SV, reproducibility is a major problem [17]. Settings of US machines and the scanning technique of the sonographer can greatly influence the visualization of SV, which affects reproducibility. Among the various US machine settings, US parameters such as pulse repetition frequency influence the quality of PDS imaging. Further, deterioration of the US transducer can adversely affect PDS imaging. Thus appropriate machine settings and maintenance are critical to ensure stable and reproducible PDS imaging. To minimize problems of the scanning technique, standardization of joint scanning has been studied by the EULAR [18, 19]. Education of the sonographer and proficiency in scanning are important for stable PDS imaging and improves reproducibility.

To measure SV by PDS, a semi-quantitative scoring system has been described [20] that comprises four scoring categories (0, none; 1, mild; 2, moderate; 3, severe) determined by the area of SV and grossly scored from the PDS images. This simple method has the advantage of no requirement for additional devices or special software, but reproducibility and reliability are problematic. Several clinical trials, most performed by members of the EULAR, have addressed these issues [21–24]. These studies found that appropriate training in scanning technique and reading of PDS images could improve and stabilize the reproducibility and reliability of scoring. However, this semi-quantitative scoring system might not be satisfactory to assess joint inflammation because it includes only four scoring categories. Therefore quantitative methods were established to measure SV in more detail [25–27]. Several groups reported a quantitative method to measure pixel counts of SV in the region of interest, which was located at in synovial tissue. Quantitative measurement could show the level or changes of SV numerically.

Because US is fundamentally a two-dimensional (2D) assessment, the images reflect a cross section of volumetric synovial tissue. Therefore the question of a discrepancy between sonographic assessment and the level of practical inflammation always exists. Recently three-dimensional (3D) PDS has been developed that enables assessment of SV at a volumetric level [28, 29]. This method may have several advantages, including image reproducibility and fewer training requirements for scanning joints or reading images. Naredo *et al.* [30] reported that 3D PDS showed repeatability such that it could be used in multicentre cohort studies of RA.

Abnormal SV in the early diagnosis of RA

Because abnormal SV is strongly associated with the pathology of synovitis, logically, detecting abnormal SV at symptomatic joints may be useful for proving the presence of synovitis and in finally diagnosing RA. We previously reported that when the sum of the levels of SV at the finger joints in each undiagnosed patient exceeded a certain level, the patient was ultimately diagnosed as having RA [31]. This result indicated the potential for detection of SV to become a first-stage screening test for RA. Importantly, diagnosis of RA requires not only detection of synovitis, but also systemic evaluation including serological or clinical tests.

The new 2010 ACR/EULAR classification criteria for RA were introduced with the aim of diagnosing RA earlier than with conventional methods [15, 16]. Attempts to combine the 2010 ACR/EULAR classification criteria with detection of synovitis by US to improve diagnostic power were reported from several groups [32–34]. Kawashiri *et al.* [33] reported that positive signs of sonographically abnormal SV in patients with undefined arthritis were a stronger prognostic factor for developing RA than were MRI findings or the presence of sonographic synovial hypertrophy. Nakagomi *et al.* [34] reported that US findings, including positive SV, had the power to confirm the presence of synovitis and increased the accuracy of the classification criteria. Thus, in the early diagnosis of RA, detection of abnormal SV has the potential to be used as a screening test or to confirm clinical findings.

Change in SV for assessment of overall disease activity in RA

Estimation of SV can be useful for assessment of disease activity in RA [35]. Although the semi-quantitative scoring system comprises only four categories, and thus is inadequate to assess changes in local joints, it could be useful for assessment of overall disease activity in combination with US estimation at several joints. US-based global scores aimed at assessing overall disease activity consist of the synovial hypertrophy score and SV score. These