Choice of the most appropriate biological disease-modifying anti-rheumatic drug for injection spacing: results from a multicentre observational study

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Abstract

Objective

To determine which biological disease-modifying anti-rheumatic drug (bDMARD) is most appropriate for spacing in patients with rheumatoid arthritis (RA) who have persistent stable symptoms.

Methods

In patients with sustained low disease activity (LDA) or better for ≥3 months who were treated with bDMARDs, the interval between bDMARD injections was extended 1.5 times, and treatment continuation rates at 104 weeks were calculated for each drug. Patients who discontinued therapy owing to adverse reactions and those who withdrew for reasons unrelated to the drugs were excluded. Whether patients could remain in LDA or better after injection spacing was investigated. The targeted drugs were an anti-tumour necrosis factor (TNF) inhibitor (golimumab [GOL]) and 2 non-TNF inhibitors (tocilizumab [TCZ] and abatacept [ABT]).

Results

The spacing evaluation included 57, 93, and 40 patients who received GOL subcutaneous injection (SC), TCZ (SC in 21 and drip intravenous injection [DIV] in 72), and ABT (SC in 12 and DIV in 22), respectively. At 104 weeks, the number of patients who discontinued therapy owing to adverse reactions did not significantly differ among the drugs. At 104 weeks, the treatment continuation rate was 0.71 for TCZ SC, 0.70 for GOL, 0.69 for TCZ DIV, 0.55 for ABT SC, and 0.50 for ABT DIV. The continuation rate for ABT was significantly lower than those for GOL and TCZ. No significant difference in continuation rates was observed between SC and DIV.

Conclusion

When the injection interval was extended, GOL and TCZ were superior to ABT in terms of continuation rate.

Key words

rheumatoid arthritis, biological agent, spacing, continuation ratio, tapering, clinical study

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Received on November 7, 2018; accepted in revised form on June 10, 2019.

Competing interests: none declared.

Introduction

Since the advent of biological disease-modifying anti-rheumatic drugs (bDMARDs), the treatment of rheumatoid arthritis (RA) has dramatically advanced. At present, RA remission can be expected. However, the cost of bDMARD is high, limiting the use for all patients. Accordingly, the European League Against Rheumatism (EULAR) has issued recommendations that support tapering of drug doses and spacing of injections in patients who remain in low disease activity (LDA) (1). In another attempt to reduce drug costs, cheaper biosimilar DMARDs (bsDMARDs) have recently been introduced (2). These bsDMARDs have been confirmed to be equivalent to bio-original DMARDs (boDMARDs) in terms of efficacy and safety (3-6). According to EULAR recommendations, when the efficacy of a boDMARD is insufficient, the use of a bsDMARD in the same class is not approved. However, the recommendations indicate that bsDMARDs approved by the European Medical Agency (EMA) or the Food and Drug Administration (FDA) can be used in the same way as boDMARDs in patients who respond to boDMARDs (1). bsDMARDs are marketed after expiration of patents of boDMARDs. Thus, bsDMARDs are not available for all currently marketed boDMARDs and are not marketed for a certain period until patent expiration.

Thus, spacing of boDMARD injections appears to be an important strategy to reduce healthcare costs incurred by patients treated with boDMARDs. Although this strategy has been reported to be effective for reducing healthcare costs (6), another report concluded that it is unlikely to be useful because spacing may lead to flares of RA activity (7). Edwards et al. reported that the success rates of spaced boDMARD therapy vary and continuation rates differ depending on whether a patient has early or established RA (9). However, further studies are needed to confirm their findings.

The continuation rate in spacing biological agents is mostly related to TNF biologics (10) but rarely to non-TNF biologics (11-14). A meta-analysis study did not report a comparison between TNF and abatacept (15). No previous report directly compared TNF and non-TNF agents. In recent years, because of the diversification of therapeutic strategies, non-TNF inhibitors have been used as the first boDMARD, depending on patient conditions, in an increasing number of cases (1, 16, 17).

This multicentre clinical study aimed to assess the effect of spacing bDMARD injections and evaluated 3 drugs, including a TNF inhibitor (golimumab [GOL]) and 2 non-TNF inhibitors (tocilizumab [TCZ] and abatacept [ABT]).

Materials and methods

Study design

This observational multicentre clinical study was conducted in patients with established RA in whom at least 6 months had passed since RA had been diagnosed on the basis of the 1987 or 2010 RA classification criteria (18). Of the patients who visited medical institutions specialising in the treatment of RA (Matsuno Clinic for Rheumatic diseases, Katayama Orthopedic Rheumatology Clinic, and Matsubara Mayflower Hospital), between February 2014 and January 2017, those scheduled to begin treatment with one of the 3 bDMARDs (GOL, TCZ, or ABT) were tentatively registered (at registration), and the study commenced. Although no particular exclusion criteria were used regarding treatment administered before registration, patients who had been treated with any of the 3 drugs were excluded. After initiation of treatment with any of the 3 drugs, patients who remained in LDA (defined as a 28-joint disease activity score using erythrocyte sedimentation rate [DAS28-ESR] of <3.2 according to the EULAR) for at least 3 months (19) were formally registered (at spacing) and included in the analyses (Fig. 1). This formally registered patient group was set as a safety evaluation group. For the patients formally registered in this study, the bDMARD injection interval was extended to 1.5 times the standard interval, and the drugs were compared and analysed (GOL, 6 w; ABT SC, 10 d; ABT DIV, 6 w; TCZ SC, 3 w; TCZ DIV, 6 w; subcutaneous [SC] and intravenous drip [DIV]). Written consent for participa-

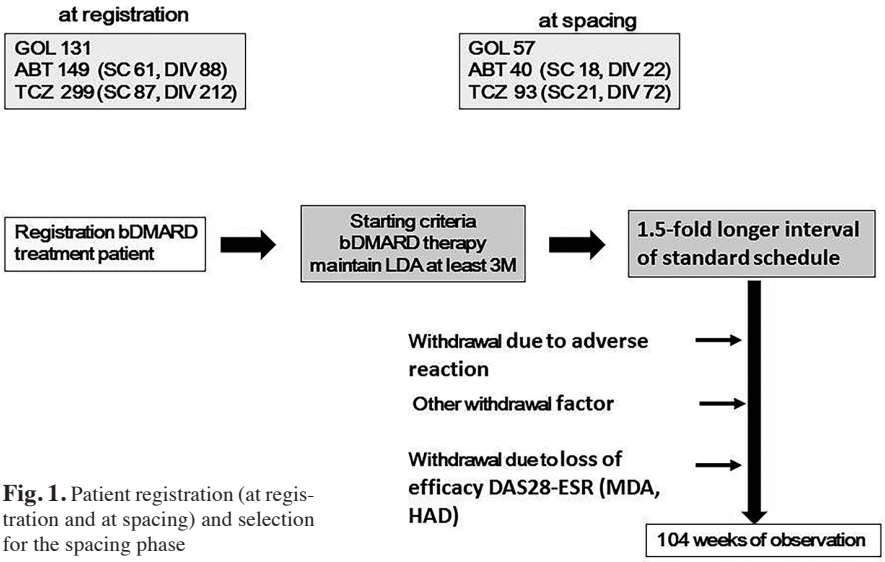

Fig. 1. Patient registration (at registration and at spacing) and selection for the spacing phase

Table I. Demographic and disease charcteristics of patients of spacing.

At spacing	GOL(n=40)	ABT(n=22)	TCZ(n=65)	*p*-value
Age	58.2 ± 5.40	72.7 ± 7.61	58.8 ± 14.6	$p<0.001$
Disease duration (y)	6.93 ± 7.34	13.7 ± 13.6	8.09 ± 6.81	$p<0.001$
DAS28-ESR	1.93 ± 0.46	2.04 ± 0.37	1.95 ± 0.49	$p=0.629$
CDAI	6.10 ± 0.83	6.50 ± 0.47	6.08 ± 2.67	$p=0.680$
CRP (mg/dl)	0.49 ± 0.26	0.65 ± 0.69	0.16 ± 0.36	$p<0.001$
MTX (mg/w)	8.60 ± 4.82	9.00 ± 2.81	8.15 ± 3.05	$p=0.612$

tion in this study was obtained from each patient at the time of tentative registration. The study protocol was approved by the ethics committee of Matsubara Mayflower Hospital (approval no. 17-03, Mar 8, 2017). The follow-up period was set at 104 weeks. A patient population that excluded patients who discontinued the therapy owing to adverse reactions or factors unrelated to biologics from the formally registered patient group during the follow-up period was set as the efficacy evaluation group. Patients whose disease activity progressed to moderate or worse (moderate disease activity [MDA], DAS28-ESR ≥3.2) (19) after injection spacing were regarded as withdrawn from the therapy in this study. In such patients, injection spacing was reverted to the standard interval.

Clinical examination items

In patients formally registered in the spacing phase of this clinical study, the temporal changes in DAS28-ESR and clinical disease activity index (CDAI) (20) during the 104-week follow-up period were assessed. Regarding radiographic assessment, according to our previous report (17), modified total sharp scores (mTSSs) were calculated on radiographs taken at the start of the spacing phase and the end of the 104-week follow-up period. The definitions of structural remission (ΔmTSS ≤0.5) and rapid radiographic progression by 8% (ΔmTSS ≥5), as well as the criteria for reading and interpretation of radiographs, were based on our previous report (17). For radiographic assessment, mTSSs were calculated by physicians who were blinded to the radiography dates and did not participate in the present clinical study. The treatment continuation rates were analysed using the Kaplan-Meier method. The first end point of this study was the continuation rate after spacing. The other end points were DAS28-ESR, CDAI, modified sharp score, and incidence of adverse events.

Statistical analyses

Differences in patient backgrounds among the 3 drug groups (GOL *vs*. ABT *vs*. TCZ) were analysed using one-way analysis of variance (ANOVA) for numerical variables and the Fisher exact test for binominal variables. CDAI and DAS changes from 0 week to 104 weeks during spacing were compared among the 3 drug groups and analysed using a general linear-model multivariate analysis. DAS28 and CDAI at registration and spacing were compared using a paired *t*-test in each treatment. The treatment continuation rates at 104 weeks was statistically analysed with the Fisher exact test. All statistical analyses were performed using R v. 3.2.2 (2015-08-14).

Results

Differences in the backgrounds of the patients treated with bDMARDs at spacing

Table I shows the patients' backgrounds. The one-way ANOVA revealed that age, disease duration, and C-reactive protein (CRP) level were significantly different when the mean values among the 3 groups were compared for baseline data at the time of spacing treatment according to each factor. Therefore, a multivariate analysis was performed using a general linear model with the above-mentioned 3 factors as covariates, with the changes in DAS and CDAI (difference in value between 104 weeks and 0 week) as the objective variables (Table I).

Study discontinuation due to adverse reactions and other reasons

Besides loss of efficacy, Table II shows why and when patients discontinued participation in this study. Including the patients with reasons enclosed in parentheses in the Table, which appeared unlikely to be related to the drugs, those who discontinued treatment because of adverse reactions were excluded from the analyses for the spacing phase. In addition to the patients excluded because of adverse reactions, the following patients were also excluded: those in the GOL group who developed influenza and those in the ABT group who discontinued the spaced therapy because they underwent surgery or family members developed tuberculosis (the patients had no tuberculosis). The incidence of adverse events was

Table II. Adverse events

	0	12	24	52	104 weeks
GOL	hives 1 erythema 1 2	high fever 1 itch 1 2	pregnancy 1 1	pneumonia 1 (influenza 1) 1(1)	total 5
ABT	hypotension 1 bronchitis 1 2	0 0	(ope. 1) (1)	pneumonia 1 (ope. 2) (family TB 1) 1(3)	total 3
TCZ	cellulitis 2 herpes zoster 1 bronchitis 1 4	pneumonia 2 2	leukopenia 1 high fever 1 2	cellulitis 1 herpes zoster 1 pneumonia 1 leukopenia 1 4	total 12

Adverse reactions and the time of onset according to bDMARD assignment.
In addition, bDMARD therapy with a spaced interval cannot be continued in all patients, regardless of type of bDMARD. This should be taken into consideration as a limitation of the spacing strategy.

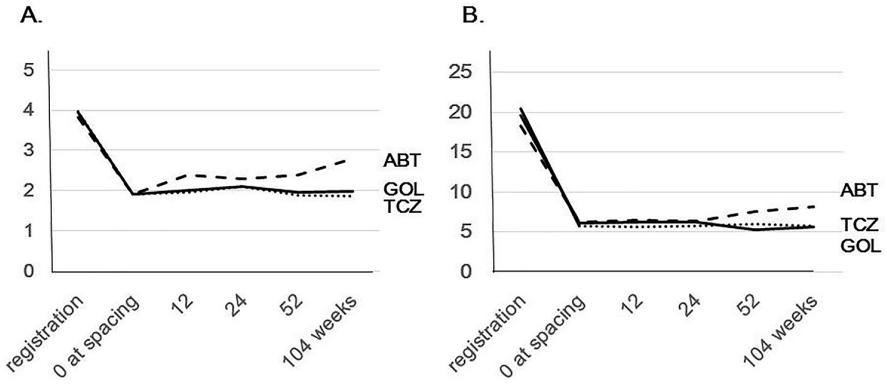

Fig. 2. Time course of changes in DAS28-ESR (**A**) and CDAI (**B**).

Table III. Comparison of CDAI change from baseline to 104 weeks during spacing among the 3 drug groups (GOL, ABT, TCZ).

	Df	Sum Sq	Mean Sq	F value	*p*-value
Factor (group)	2	77.69	38.844	3.904	0.02275
Age	1	1.68	1.684	0.1692	0.68151
Disease duration	1	23.7	23.696	2.3815	0.12539
CRP	1	11.69	11.686	1.1745	0.28064
Residuals	121	1203.93	9.95		

Significantly different results were obtained when multivariate analysis was used to study the amount of change in CDAI among the three groups, excluding the effects of age, disease duration and CRP. Also, age, onset and CRP of covariate, did not significantly affect changes in CDAI.
Df: degree of freedom; Sq: square.

0.072 person-years (95% confidence interval, 0.015–0.129 person-years) in the GOL group, 0.066 person-years (0.086–0.234 person-years) in the ABT group, and 0.077 person-years (0.030–0.124 person-years) in the TCZ group. The 95% confidence intervals of the incidence rates in the 3 groups are nearly overlapping. Therefore, the incidence rates did not significantly differ among the 3 groups.

Clinical course

After registration at the start of bDMARD therapy, the patients who remained in LDA or better for ≥3 months included 57 (43.5%) of the 131 patients in the GOL group, 40 (26.8%) of the 149 patients in the ABT group, and 93 (31.1%) of the 299 patients in the TCZ group. In all the drug groups, DAS28-ESR was significantly lower at the start of the spacing phase than at the start of the bDMARD therapy phase ($p<0.001$; Fig. 2A.B). Changes in DAS28 from 0 week to 104 weeks during spacing among the 3 drug groups (GOL *vs*. ABT *vs*. TCZ) are compared in Table III. The change in DAS28 significantly differed among the 3 groups, excluding the effects of age, disease duration, and CRP level, in the multivariate analysis. In addition, age and disease duration did not significantly affect the change in DAS28, but CRP level significantly affected the change in DAS28. Table IV shows a comparison of the CDAI changes from 0 week to 104 weeks during spacing among the 3 drug groups (GOL *vs*. ABT *vs*. TCZ). Significantly different results were obtained when a multivariate analysis was used to study the amount of change in CDAI among the 3 groups, excluding the effects of age, disease duration, and CRP level. In addition, age, onset, and CRP level as covariates did not significantly affect the changes in CDAI. Therefore, the spacing effect of ABT might be less than that of the other 2 bDMARDs (GOL and TCZ).

Changes in radiographic findings

The proportions of patients who showed structural remission and rapid radiographic progression were, respectively, 84% (21/25) and 4% (1/25) in the GOL group, 73% (11/15) and 13% (2/15) in the ABT group, and 78% (36/46) and 8% (4/46) in the TCZ group. No significant differences in radiographic progression were observed among the drug groups (Fig. 3).

Continuation rates of the bDMARD therapies

After the interval between the bDMARD injections was extended to 1.5 times the standard interval, no significant differences in treatment continuation rates were observed during the first 36 weeks among the drug groups. However, at 104 weeks, the rates remained significantly higher in the GOL and TCZ groups than in the ABT group ($p<0.001$; Fig. 4). The flare rate was 30% for GOL, 29% for TCZ SC, 31% for TCZ IV, 45% for ABT SC, and 50% for ABT IV. When the continuation rates were also compared between the 2

Table IV. Comparison of DAS change from baseline to 104 weeks during spacing between the 3 drug groups (GOL, ABT, TCZ).

	Df	Sum Sq	Mean Sq	F value	*p*-value
Factor (group)	2	5.593	2.79627	8.6309	0.00031
Age	1	0.485	0.48496	1.4969	0.22353
Disease duration	1	0.017	0.01672	0.0516	0.82067
CRP	1	1.418	1.41795	4.3766	0.03853
Residuals	121	39.202	0.32398		

It was significantly different when examining the amount of change in DAS between the three groups, excluding the effects of age, disease duration and CRP by multivariate analysis. In addition, age and disease duration did not significantly affect changes in DAS, but CRP significantly affected the change in DAS. Df: degree of freedom; Sq: square.

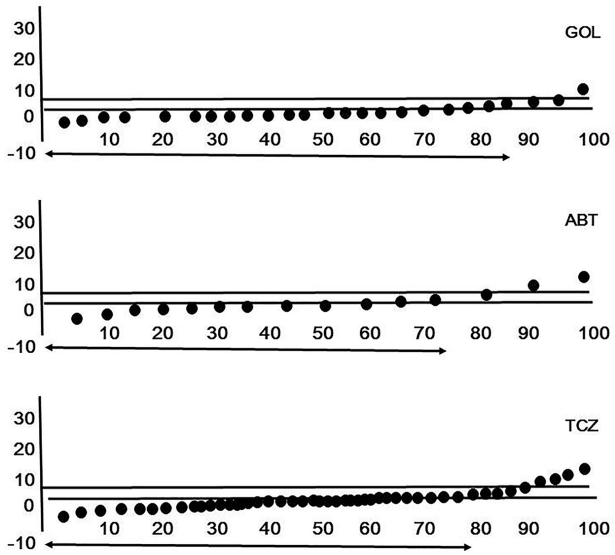

Fig. 3. Cumulative probability plot of radiological progression (ΔmTSS). Arrows: structural remission of radiological damage.

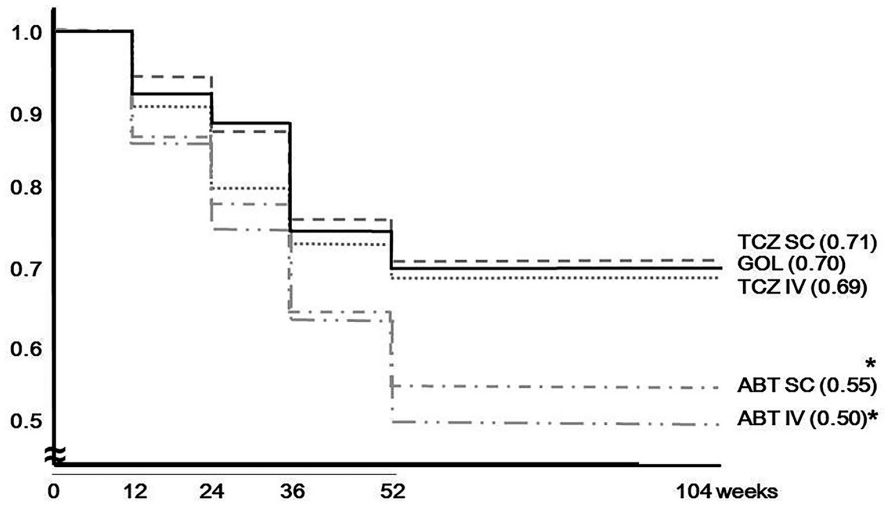

Fig. 4. Treatment continuation rate (Kaplan-Meier estimator). The number in the parentheses shows the survival rate with each treatment at 104 weeks.

types of administration routes used for TCZ and ABT, no significant difference was observed between SC and DIV.

Discussion

bDMARDs are effective for RA, but their high cost limits their use. Thus, permanent treatment is impractical from the perspective of medical economics (20). Even though disease activity in RA can decrease to remission with bDMARDs, discontinuation of the drugs is difficult (21). Many randomised controlled trials have demonstrated that instead of discontinuation of bDMARDs, spacing is a better strategy after achievement of remission or LDA (22). Thus, studies have been conducted to determine whether the use of bsDMARDs (3-6), and tapering and spacing of boDMARD are practical and effective methods for reduction of drug costs (7, 8). Although it has been demonstrated to be effective for reducing costs (23), spacing has not been sufficiently investigated to determine which bDMARD is most appropriate for spacing or what degree of spacing is appropriate.

Thus, in the present study, 3 bDMARDs with different actions were selected and compared for treatment continuation rates after spacing. The selected bDMARDs were a TNF inhibitor (GOL) and 2 non-TNF inhibitors (an interleukin-6 inhibitor [TCZ] and a T-cell inhibitor [ABT]). The effects of spacing were analysed in the patients treated with the 3 drugs at multiple medical institutions. In the Spacing of TNF-blocker Injections in Rheumatoid Arthritis Study, which retrospectively analysed outcomes of extended spacing, the rates of sustained remission did not reach 50% in patients treated according to a study design in which injections were spaced out to a maximum of 3 times the standard interval or discontinued (24). By contrast, the success rate of spacing was relatively high in the patients treated at an interval extended to 1.5 times the standard interval (designed as step 1). On the basis of these results, the interval between injections was extended to 1.5 times the standard interval, and the treatment continuation rates after spacing were compared among the 3 types of bDMARDs in the present study. As a result, the continuation rates were higher for GOL and TCZ than for ABT.

As the present clinical study was not a randomised controlled trial, the patient backgrounds were not completely matched. As for the possible reasons why the patients treated with ABT were significantly older at the time of tentative registration than those treated with the other drugs, ABT has been reported to be associated with a low incidence rate of infection, which is a common

adverse reaction in elderly patients, and is as effective in elderly patients with RA as in younger patients with RA (25, 26). However, because no statistically significant differences were observed in any other items, the patient groups compared in the present clinical study seem appropriate for analysing treatment continuation rates relevant to the actual clinical practice. At the start of the spacing phase, the proportion of patients concomitantly treated with MTX and the CRP levels were statistically significantly lower in the TCZ group than in the other drug groups. This was assumed to be attributable to the pharmacological actions of TCZ (16, 27).

On the basis of DAS28-ESR and CDAI, GOL and TCZ were therapeutically more effective than ABT at 24 weeks and remained so afterward. As GOL and TCZ are ranked higher than ABT in terms of efficacy (28, 29), the present study appears to have yielded similar results.

The difference in the efficacy of the drugs might have contributed to the significantly higher treatment continuation rates shown at 104 weeks in the GOL and TCZ groups than the rates in the ABT group. Furthermore, the 2 drugs with high treatment continuation rates are also associated with a low frequency of anti-drug antibodies (30, 31). In terms of immunogenicity, a low possibility of secondary ineffectiveness might have also contributed to the prolonged period of high treatment continuation rate. As the present study showed that the treatment continuation rates after spacing of bDMARD injections varied among the targeted drugs, assessment of treatment continuation rates for all currently marketed bDMARDs seems necessary in the future. Such studies may also need to be conducted with a large sample of patients with similar backgrounds.

Absolute comparison was not performed because the study was an observational research. Direct effects and safety could not be compared under the same condition. The spacing effect of the biological agents were confirmed in many RA patients at intervals extended <1.5 times. The difference in effect was found to be dependent on the selected biological agents. Biological agents should be carefully selected according to the patient's condition and background.

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