Original Article

Predictors of biologic discontinuation due to insufficient response in patients with rheumatoid arthritis who achieved clinical remission with biologic treatment: a multicenter observational cohort study

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Abstract

Objective: This study aimed to investigate predictors of biologic discontinuation due to insufficient response as a surrogate for relapse in patients with rheumatoid arthritis (RA) who achieved clinical remission with biologic treatment.

Methods: This study was performed based on data from a multicenter registry, and included 404 patients who achieved clinical remission within the first year of treatment with their first biologic. Cumulative retention rate of the first biologic was estimated using Kaplan-Meier curves, and the impact of patient characteristics on biologic discontinuation was assessed with Cox proportional hazards models.

Results: During follow-up, 50 patients discontinued their first biologic due to insufficient response. Overall discontinuation rates due to insufficient response after achieving remission were 6%, 11%, and 19% at 1, 2, and 5 years, respectively. Multivariate analysis revealed that concomitant glucocorticoids at achieving remission [hazard ratio (HR): 3.80, 95% confidence interval (CI): 1.89-7.64)] and a higher level of C-reactive protein (CRP) at achieving remission (HR: 1.47 per 1mg/dL, CI: 1.09-1.99) independently predict discontinuation due to insufficient response after achieving remission.

Conclusion: Patients with RA who achieved remission with concomitant glucocorticoid treatment and a higher level of CRP are at high risk of subsequent biologic discontinuation due to insufficient response.

Introduction

The ultimate goals of rheumatoid arthritis (RA) treatment are preventing structural damage and normalizing function by sustaining clinical remission. Although newer medications including biologics and more aggressive treatment strategies have enabled more patients with RA to achieve clinical remission, sustained remission is still uncommon in clinical practice [1].

Interruption of biologics while maintaining remission—a challenge in clinical research surrounding RA—may be beneficial from the perspective of reducing adverse events and costs. Recent studies have evaluated the reduction and/or interruption of biologics in patients with RA. A meta-analysis of these studies revealed that 20 to 60% of patients with low disease activity or in remission reduced or stopped biologics without relapse within the first year [2]. Notably, however, some patients relapsed even while continuing biologic therapy in both randomized control trials (RCTs) [3, 4] and cohort studies [5, 6]. Hence, it is important to identify risks for relapse despite continuing biologic treatment.

Patients with RA discontinue biologic treatment for several reasons, including insufficient response, adverse events, and economic reasons. Drug retention and discontinuation may thus be considered a reliable indicator of overall therapeutic efficacy in observational registries. In particular, drug discontinuation rate due to insufficient response after achieving remission can serve as a surrogate for relapse. This observational cohort study

aimed to investigate predictors of biologic discontinuation due to insufficient response in patients who achieved clinical remission with biologic treatment.

Patients and Methods

Patients

This multicenter cohort study was performed based on data from the Tsurumai Biologics Communication Registry (TBCR), an RA research consortium that consists of Nagoya University Hospital and 19 affiliated institutions [7]. TBCR was initiated in October 2008 to study the long-term efficacy and safety of treatment with biologics in patients with RA. Data were collected retrospectively for patients treated prior to 2008, and prospectively from 2008 on. Registered data are updated annually and contain a great deal of information, including demographic and clinical characteristics, drug continuation, reason for discontinuation of drugs, and adverse events occurring during treatment with biologics. TBCR was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine, and registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000026558). Written informed consent was obtained from all patients. Patient anonymity was maintained during data collection, and the security of personal information was strictly controlled. This study included patients with RA who achieved clinical remission, defined as a Disease Activity Score in 28 joints using the C-reactive

protein (DAS28-CRP) of < 2.6, within the first year of treatment with their first biologic. Inclusion criteria were patients 1) who were not in clinical remission at the time of registration in TBCR; 2) who were in clinical remission with the first biologic at the first year follow-up after registration; and 3) who had subsequent clinical follow-up data available. A total of 1,423 patients who had not achieved clinical remission were started on their first biologic between January 1, 2005 and December 31, 2013. Of these, 458 (32%) were in clinical remission at the first year follow-up; 54 patients for whom subsequent clinical follow-up data were not available were excluded. Thus, a final total of 404 patients were included in this study. All patients met the 1987 American College of Rheumatology (ACR) classification criteria or the new ACR/European League Against Rheumatism (EULAR) diagnostic criteria, and received biologics according to the drug label and Japan College of Rheumatology guidelines for treatment. Decisions regarding treatment, including discontinuation of biologics, were based on physician discretion.

Data collection

The first year follow-up time point after registration was considered the baseline in this study. Demographic and clinical data included age, sex, disease duration, rheumatoid factor (RF) positivity (≥15 IU/mL), Steinbrocker stage and class, DAS28-CRP, tender joint count (TJC) and swollen joint count (SJC) on 28 joints, serum CRP levels, general health on

a visual analogue scale (GH-VAS), first biologic, and concomitant treatment with MTX and/or glucocorticoids. The date of and reason for discontinuation of the first biologic were recorded, and the reasons were classified as insufficient response, adverse events, good control, and personal reasons.

Statistical analysis

Statistical analyses were performed with SPSS version 22.0.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant. Continuous variables are expressed as median and interquartile ranges (IQR), while categorical variables are expressed as percentages. In predictive analyses, discontinuation of the first biologic due to insufficient response was used as the outcome variable, and patients were censored at the time of discontinuation of the first biologic for reasons other than insufficient response, or the day of last follow-up, whichever came first. The cumulative retention rate of the first biologic was estimated using Kaplan-Meier curves, and the log-rank test was used for comparisons between groups. The impact of baseline characteristics on discontinuation of the first biologic due to insufficient response was assessed with univariate and multivariate Cox proportional hazards models. The univariate analyses included the following variables: age, sex, disease duration, RF positivity, Steinbrocker stage (stage III+IV vs. I+II) and class (class III+IV vs. I+II), DAS28-CRP at initiation of the first biologic, DAS28-CRP and its components (TJC

and SJC on 28 joints, serum CRP levels, GH-VAS) at baseline, the first biologic (tumor necrosis factor [TNF] inhibitors vs. non-TNF biologics), and concomitant treatment with MTX and/or glucocorticoids. Variables found to be significant (P<0.05) in univariate analyses were included in the multivariate model.

Results

Patient characteristics

Baseline characteristics of all patients included in this study are shown in Table 1. Data for RF were available for 377 patients, while other data were available for all patients. The median (IQR) disease duration was 7 (3-14) years, indicating that most patients had established RA, with 250 patients (62%) being categorized as advanced Steinbrocker stages (III or IV). The proportions of patients with low, moderate, and high disease activity as assessed by DAS28-CRP score at initiation of biologics were 9%, 65%, and 26%, respectively. A total of 346 patients (86%) received TNF inhibitors, and 58 (14%) received non-TNF biologics as their first biologic. Of all patients, 321 (79%) received MTX at a median (IQR) dose of 8 (6-8) mg/week, and 202 (50%) received glucocorticoids at a median (IQR) dose of 5.0 (2.5-5.0) mg/day at baseline. The median (IQR) follow-up period from baseline was 2.5 (1.1-4.5) years.

Cumulative retention rate of biologics

During follow-up, 50, 38, 16, and 12 patients discontinued their first biologic due to insufficient response, adverse events, personal reasons, and good control, respectively. According to Kaplan-Meier estimates, overall discontinuation rates due to insufficient response were 6%, 11%, and 19% at 1, 2, and 5 years from baseline, respectively (Fig. 1a). We next estimated the discontinuation rate due to insufficient response stratified by the following baseline categorical variables: sex, RF positivity, Steinbrocker stage (I+II vs. III+IV), Steinbrocker class (I+II vs. III+IV), the first biologic (TNF inhibitors vs. non-TNF biologics), and concomitant MTX and glucocorticoids. Seven of the 154 patients (5%) at Steinbrocker stage I+II, and 43 of 250 patients (17%) at Steinbrocker stage III+IV, discontinued due to insufficient response during the follow-up period. According to Kaplan-Meier estimates, the discontinuation rate due to insufficient response for Steinbrocker stage III+IV patients was significantly higher than that for Steinbrocker stage I+II patients (24% vs. 9%, respectively, at 5 years, log-rank test, P=0.001) (Fig. 1b). Ten of the 202 patients (5%) without concomitant glucocorticoids, and 40 of 202 patients (20%) with concomitant glucocorticoids, discontinued due to insufficient response during the follow-up period. According to Kaplan-Meier estimates, the discontinuation rate due to insufficient response for patients with concomitant glucocorticoids was significantly higher than that for patients without concomitant glucocorticoids (31% vs. 6%, respectively, at 5 years, log-rank

test, $P<0.001$) (Fig. 1c). There was no significant difference in the discontinuation rate due to insufficient response stratified by sex, RF positivity, Steinbrocker class, the first biologic, or concomitant MTX.

Impact of baseline variables on biologic discontinuation due to insufficient response

Hazard ratios [HRs] for discontinuation of the first biologic due to insufficient response were calculated using Cox proportional hazards models (Table 2). Univariate analysis revealed that longer disease duration (HR: 1.04 per 1 year, 95% confidence interval [95% CI]: 1.02-1.07), Steinbrocker stage (III+IV vs. I+II) (HR: 3.39, 95% CI: 1.52-7.54), higher level of serum CRP (HR: 1.65 per 1 mg/dL, 95% CI: 1.26-2.16), and concomitant glucocorticoids (HR: 4.24, 95% CI: 2.12-8.48) predicted biologic discontinuation due to insufficient response. None of the other variables were predictive. We next performed multivariate analysis with disease duration, Steinbrocker stage, serum CRP levels, and concomitant glucocorticoids set as variables. Higher level of serum CRP (HR: 1.47 per 1 mg/dL, 95% CI: 1.09-1.99) and concomitant glucocorticoids (HR: 3.80, 95% CI: 1.89-7.64) at achieving remission independently predicted biologic discontinuation due to insufficient response.

Discussion

This cohort study investigated predictors of biologic discontinuation due to insufficient response as a surrogate for relapse in patients who achieved clinical remission with biologic treatment. In the pre-biologic era, female sex, longer disease duration, RF positivity, and disease activity have been shown as predictors of relapse [8, 9]. However, corresponding evidence concerning biologics has not been accumulated. Our multivariate analysis revealed that concomitant glucocorticoids and a higher level of serum CRP at the time of achieving remission were independent predictors of biologic discontinuation due to insufficient response after achieving remission. The present findings provide important new insights into the maintenance of remission in the biologic era.

Glucocorticoids have been used for decades in the treatment of RA. The disease modifying effect of glucocorticoids in RA has recently been reassessed. Recent RCTs clearly showed that concomitant low-dose glucocorticoids effectively increase remission rates in patients with early RA treated with synthetic disease-modifying antirheumatic drugs [10, 11]; however, little is known about differences between the sustainability of remission achieved with or without concomitant glucocorticoids, especially in patients with established RA treated with biologics. Most patients included in this study had established RA because our registry consists of patients treated with biologics in clinical practice. This study demonstrates that remission achieved with concomitant glucocorticoids is less persistent than that achieved without concomitant glucocorticoids in patients with established RA treated

with biologics. Adjustment of concomitant therapy may affect the continuation of biologic therapy in long-term clinical practice. Of the 202 patients who achieved remission with concomitant glucocorticoids in our cohort, 132 (65%) reduced or stopped glucocorticoid therapy, whereas 70 (35%) remained on therapy or increased doses after achieving remission. Thus, the proportion of biologic discontinuation due to insufficient response during the follow-up period in patients who retained or increased glucocorticoids was significantly higher than that in patients who reduced or stopped glucocorticoids (29% vs. 15%, chi-square test, P=0.027) (data not shown). This finding further supports our speculation that the sustainability of remission achieved with concomitant glucocorticoids is lower than that achieved without concomitant glucocorticoids.

An increasing number of patients with RA can now achieve remission thanks to biologics, and an issue arises as to whether biologic therapy can be tapered or stopped while maintaining remission. The guidelines of EULAR [12] and ACR [13] stress that treatment tapering must be carried out slowly and carefully. In our cohort, 19% of all patients and 31% of patients with concomitant glucocorticoids discontinued biologics due to insufficient response in the 5 years following remission. Accordingly, modulation of biologics after achieving remission should be conducted with caution, especially in patients who were taking concomitant glucocorticoids at the time of achieving remission; this supports the recent EULAR recommendations to taper glucocorticoids before tapering biologics [12].

CRP is an acute-phase protein and a marker for systemic inflammation. Serum CRP level is a single objective biomarker of disease activity in RA because it is highly responsive to changes in cytokine (TNFα)-mediated inflammation. CRP level can therefore be used to predict, assess, and monitor response to treatment with TNF inhibitors [14]. Our multivariate analysis revealed that serum CRP level at the time of achieving remission independently predicts subsequent discontinuation of biologics due to insufficient response. This finding is supported by previous studies reporting that CRP level may predict relapse in patients who achieved remission with conventional synthetic disease modifying antirheumatic drugs [15, 16]. This suggests the importance of suppressing systemic inflammation to maintain remission.

Registered data including disease activity are updated annually in our cohort, and it is impossible to grasp detailed changes in disease activity. Accordingly, in this study, discontinuation of biologics due to insufficient response after achieving remission was used as an alternative outcome for relapse. However, drug discontinuation was based on each physician's discretion and reasons for discontinuation were not clearly defined. According to previous cohort studies including patients with established RA treated with biologics, 6 to 9% of patients had relapse, defined as a DAS of >2.7 or ≥3.2, within the first year even while continuing biologic therapy [5, 6]. These studies included only a small number of patients (n=17 and 23) with follow-up periods of 1 year, while the present study included 404 patients

with a median follow-up period of 2.5 years. The discontinuation rate due to insufficient response after achieving remission in this study is comparable to the incidence of relapse reported in previous studies. Drug discontinuation rate due to insufficient response after achieving remission can thus serve as a surrogate for relapse in long-term cohort studies.

This study has some limitations worth noting. First, the registry does not include data regarding comorbidities, although comorbidities are a potential confounding factor for the selection of treatment such as concomitant use of glucocorticoids. We could not obtain sufficient data concerning RF titer, anti-citrullinated protein antibody levels, and smoking status, all of which have been reported to be prognostic factors in RA [17-19]. Second, the sample size and observation period were limited, and the significance of some of the findings may change with a larger and longer data set. Further studies with a greater sample size and follow-up period will be needed.

In conclusion, patients with RA treated with biologics who achieved remission with concomitant glucocorticoids, and had a higher level of CRP at the time of achieving remission, are at high risk of subsequent biologic discontinuation due to insufficient response. Our findings suggest that patients undergoing biologic therapy with concomitant glucocorticoids should be treated with caution, so as to prevent relapse even after achieving remission, and highlight the importance of suppressing systemic inflammation to maintain remission.

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Conflicts of interest

Y. Hirano received lecture fees from AbbVie Inc, Eisai Co, Mitsubishi Tanabe Pharma Co, Pfizer Inc, Chugai Pharmaceutical Co, and Bristol-Myers Squibb Co. A. Kaneko received lecture fees from Mitsubishi Tanabe Pharma Co, Takeda Pharmaceutical Co, Eisai Co, Chugai Pharmaceutical Co, AbbVie Inc, Bristol-Myers Squibb Co, UCB Japan Co, Janssen Pharmaceuticals, and Pfizer Inc. N. Takahashi received lecture fees from AbbVie Inc, Eisai Co, UCB Japan Co, Mitsubishi Tanabe Pharma Co, Takeda Pharmaceutical Co, Pfizer Inc, Chugai Pharmaceutical Co, Janssen Pharmaceuticals, and Bristol-Myers Squibb Co. N. Ishiguro received grants and lecture fees from Daiichi Sankyo Co, Takeda Pharmaceutical Co, Hisamitsu Pharmaceutical Co, Otsuka Pharmaceutical Co, Taisho Toyama Pharmaceutical Co, Kaken Pharmaceutical Co, Eisai Co, Janssen Pharmaceuticals, Bristol-Myers Squibb Co, AbbVie Inc, Chugai Pharmaceutical Co, Mitsubishi Tanabe Pharma Co, Astellas Pharma Inc, and Pfizer Inc. T. Kojima received lecture fees from Mitsubishi Tanabe Pharma Co, Takeda Pharmaceutical Co, Eisai Co, AbbVie Inc, Bristol-Myers Squibb Co, Pfizer Inc, Janssen Pharmaceuticals, Astellas Pharma Inc, and Chugai Pharmaceutical Co. The other authors declare no conflicts of interest.

Table 1. Baseline characteristics of patients

	n = 404
Age, years	57 (46-66)
Female, %	85
Disease duration, years	7 (3-14)
RF positive, %[a]	81
Steinbrocker stage III+IV, %	62
Steinbrocker class III+IV, %	15
DAS28-CRP at initiation of biologics	4.5 (3.8-5.2)
DAS28-CRP at baseline	2.0 (1.5-2.3)
Tender joint count (0-28 scale)	0 (0-1)
Swollen joint count (0-28 scale)	0 (0-1)
CRP, mg/dL	0.10 (0.03-0.23)
GH-VAS, 0-100 mm	14 (8-26)
TNF inhibitors, %	86
Concomitant methotrexate, %	79
Methotrexate dosage, mg/week[b]	8 (6-8)
Concomitant glucocorticoids, %	50
Glucocorticoid dosage, mg/day[c]	5.0 (2.5-5.0)

Data are presented as median (interquartile range), unless otherwise stated. RF = rheumatoid factor; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein; GH-VAS = general health on a visual analogue scale; TNF = tumor necrosis factor.

[a]Data were available for 377 patients. [b]Median among patients receiving the drug. [c]Prednisolone mg/day or equivalent. Median among patients receiving the drug.

Table 2. Impact of baseline variables on biologic discontinuation due to insufficient response

Variables	Continue n=354	Discontinue n=50	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age, years	58 (46-66)	57 (48-63)	1.00 (0.98-1.02)[a]	-
Female, %	84	90	1.13 (0.45-2.86)	-
Disease duration, years	7 (2-14)	10 (6-21)	1.04 (1.02-1.07)[a]*	1.03 (1.00-1.06)[a]
RF positive, %	81	83	1.08 (0.50-2.31)	-
Steinbrocker stage III+IV, %	58	86	3.39 (1.52-7.54)*	2.24 (0.95-5.26)
Steinbrocker class III+IV, %	14	18	1.22 (0.59-2.52)	-
DAS28-CRP at initiation of biologics	4.5 (3.8-5.1)	4.5 (4.0-5.3)	1.02 (0.76-1.35)[a]	-
DAS28-CRP at baseline	2.0 (1.5-2.3)	2.1 (1.7-2.4)	1.55 (0.85-2.84)[a]	-
Tender joint count (0-28 scale)	0 (0-1)	0 (0-1)	1.04 (0.75-1.45)[a]	-
Swollen joint count (0-28 scale)	0 (0-1)	0 (0-1)	0.82 (0.63-1.07)[a]	-
CRP, mg/dL	0.09 (0.03-0.23)	0.16 (0.08-0.32)	1.65 (1.26-2.16)[a]*	1.47 (1.09-1.99) [a]*
GH-VAS, 0-100 mm	14 (7-25)	18 (10-30)	1.02 (1.00-1.04)[a]	-
TNF inhibitors, %	85	92	1.32 (0.47-3.69)	-
Concomitant methotrexate, %	79	86	1.69 (0.76-3.75)	-
Concomitant glucocorticoids, %	46	80	4.24 (2.12-8.48)*	3.80 (1.89-7.64)*

Data are presented as median (interquartile range), unless otherwise stated. HR = hazard ratio; 95% CI = 95% confidence interval; RF = rheumatoid factor; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein; GH-VAS = general health on a visual analogue scale; TNF = tumor necrosis factor.

[a]HR for 1-unit increase in each item. *P value < 0.05.

Figure legends

Figure 1. Cumulative retention rate of biologics

Kaplan-Meier estimates of overall discontinuation rate due to insufficient response (**a**), and discontinuation rate due to insufficient response stratified by Steinbrocker stage (**b**) and concomitant glucocorticoids (GC) (**c**).

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