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ORIGINAL ARTICLE

Association between seropositivity and discontinuation of tumor necrosis factor inhibitors due to ineffectiveness in rheumatoid arthritis

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Abstract

Introduction/objectives Discontinuation of biologic therapy in rheumatoid arthritis is attributable to various reasons, with the most important cause being insufficient response. In this study, we investigated the association between rheumatoid factor (RF) and anti-citrullinated protein autoantibody (ACPA) status and the discontinuation of tumor necrosis factor inhibitors (TNFi) therapy due to insufficient response in bio-naïve rheumatoid arthritis (RA) patients.

Method This study included patients enrolled in the Tsurumai Biologic Communication Registry in Japan. The crude comparison of TNFi discontinuation due to ineffectiveness between seropositive and seronegative patients was analyzed using the cumulative incidence function of competing events and Gray test. We assessed the associations between baseline patient characteristics and discontinuation of TNFi therapy due to insufficient response using Fine-Gray proportional hazard regression. Fine-Gray proportional hazard analysis considered competing events of interest, including insufficient response, adverse event, palliation, and personal reasons.

Results Of 1237 patients evaluated, 79.3% were positive for RF and 85.4% for ACPA; 72.6% were double positive and 11.1% were double negative. TNFi therapy had been discontinued because of insufficient response at 200 weeks in 19.8% RF-positive, 16.7% RF-negative, 23.0% ACPA-positive, and 13.8% ACPA-negative patients. There was a significantly higher discontinuation rate due to insufficient response in ACPA-positive patients than in ACPA-negative patients using Gray test, with a similar trend as that for RF status. RF positivity was significantly predictive of the discontinuation of TNFi therapy due to ineffectiveness using Fine-Gray proportional hazard regression analysis after adjusting for baseline characteristics, including age, sex, stage, class, disease activity at baseline, methotrexate use, and prednisolone use [hazard ratio 1.73 (95% confidence interval 1.07–2.80)].

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Conclusions Using Fine-Gray proportional hazard regression, we demonstrated that RF positivity was related to a higher discontinuation rate of TNFi therapy due to ineffectiveness in bio-naïve RA patients.

Key Points

- *RF positivity is related to a higher discontinuation rate of TNFi therapy due to ineffectiveness.*
- *ACPA is not predictive of a discontinuation of TNFi therapy due to ineffectiveness.*

Keywords Biological therapy · Rheumatoid factor · Tumor necrosis factor · Survival analysis

Introduction

Rheumatoid factor (RF) and anti-citrullinated protein autoantibody (ACPA) are often utilized as crucial aids for the diagnosis of rheumatoid arthritis (RA) [1]. These autoantibodies may also be useful prognostic factors [2] because seropositivity is associated with the radical progression of joint destruction [3]. Recent studies have reported that long-term response to the inhibition of T cell costimulation by abatacept (ABA) was stronger in patients with ACPA [4–6]; however, the influence of these autoantibodies on the long-term efficacy of tumor necrosis factor inhibitors (TNFi) is controversial [7–9]. Therefore, we conducted an exploratory study in a large cohort of RA patients to evaluate the relationship between RF and ACPA status and the discontinuation of TNFi treatment due to ineffectiveness in a clinical setting.

Moreover, the presence of competing risks must be considered while assessing the effect of prognostic factors on the incidence of an outcome over time [10–13]. A competing risk is an event, the occurrence of which precludes the occurrence of the event of interest [14]. For instance, when evaluating the effect of risk factors on the incidence of discontinuation of biologic therapy due to insufficient response, that due to adverse events serves as a competing risk. In this study, we introduced Fine-Gray proportional hazard regression analysis that allows us to model the effects of covariates on the cumulative incidence function in the presence of competing risks.

Materials and methods

Study design and patient population

This study included patients enrolled in the Tsurumai Biologic Communication Registry (TBCR) that comprises the Nagoya University and 18 affiliated institutions in Japan. TBCR was a Japanese observational multicenter cohort study that evaluated drug retention, effectiveness, and adverse events in RA patients who had undergone biologic therapy [15]. Data were collected retrospectively for patients who started TNFi therapy from January 2004 to September 2008 and prospectively for those who started the therapy from October 2008 to December 2014. Relevant data were updated annually and contained extensive information about demographic characteristics, continuation of biologic therapy, reason for discontinuation of biologics, and adverse events. This study enrolled Japanese bio-naïve RA patients older than 18 years of age, who fulfilled the 1987 American College of Rheumatology (ACR) classification criteria or the 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis [1, 16, 17], and for whom TNFi therapy that included adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab was prescribed. Patients for whom data of neither RF nor ACPA were available and those with missing data on the therapy duration of TNFi were excluded. TBCR was executed as per the Declaration of Helsinki [18]. 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). A documented informed consent was acquired from all relevant RA patients.

Treatment

Patients were treated with TNFi monotherapy or combination therapy with conventional DMADRS, such as MTX, PSL, and tacrolimus. Rituximab is not indicated for the treatment of RA in Japan. Patients were evaluated by their rheumatologist at baseline and at least once every 3 months or more often, as needed. The type and dosage of antirheumatic therapy were chosen according to the clinical judgment of the attending rheumatologist. TNFi was administered as adalimumab 40 mg by subcutaneous injection every other week, an initial subcutaneous dose of certolizumab pegol 400 mg, followed by additional doses at weeks 2 and 4, and then 200 mg every other week; etanercept 50 mg subcutaneous injection once weekly; subcutaneous golimumab 50 mg with MTX or 100 mg subcutaneous golimumab without MTX every 4 weeks; intravenous infliximab 3 mg/kg at baseline, followed by the standard regimen. Most patients received 6–12 mg oral MTX once weekly. Throughout the study period, changes in the type and dose of concomitant

conventional DMARDS were permitted at the discretion of the attending physician.

Outcomes

Relevant data of TNFi exposure were collected, and the reasons of discontinuation of TNFi treatment were classified as insufficient response, adverse events, palliation, and personal reasons at any follow-up visit. Time to discontinuation was defined as the duration between the initiation of TNFi therapy and the last prescription. Data on patients lost to follow-up were censored at the last visit. The primary study endpoint was persistence of first-line TNFi treatment defined as the interval between drug initiation and discontinuation because of insufficient response. Secondary end points were the remission rate at 12 months determined by the disease activity score in 28 joints determined by the erythrocyte sedimentation rate (DAS28ESR) and the EULAR response of good or moderate at 12 months [19]. DAS28ESR scores ranged from 0 to 10, with scores of ≤ 3.2 indicating low, 3.2–5.1 moderate, and > 5.1 high-disease activity. In addition, a score of < 2.6 indicated clinical remission [20].

Statistical analyses

Comparisons of the baseline characteristics of RF-positive and RF-negative groups were made using chi-squared test for categorical variables and *t* test for quantitative variables. The crude comparison of TNFi treatment discontinuation due to ineffectiveness between seropositive and seronegative patients was analyzed using the cumulative incidence function of competing events and Gray test [21]. The impact of RF and ACPA on TNFi discontinuation was assessed using Fine-Gray proportional hazard regression with adjustment for potential confounders [14, 22] that included RF or ACPA positivity, age, sex, Steinbrocker stage, Steinbrocker class, DAS28ESR at baseline, methotrexate (MTX) use, and prednisolone (PSL) use. Results are presented as hazard ratio (HR) with 95% confidence interval (CI) and *p* values. HR > 1 indicates a higher likelihood of TNFi discontinuation due to ineffectiveness, while an HR < 1 indicates a lower likelihood of discontinuation. The proportions of patients with DAS28ESR remission and good or moderate EULAR responses in seropositive and seronegative patients were compared with Fisher's exact test. Multivariate logistic regression of each covariate was adjusted for confounders, and ORs of each covariate were calculated with their 95% confidence intervals (CIs).

All the analyses were conducted in EZR version 1.36 [23]. *p* values < 0.05 were considered statistically significant.

Results

Patient characteristics

We identified total 2757 RA patients for whom biologic treatment had been initiated, representing 5741 patient-years of follow-up [median 2.02 years per patient (interquartile range 0.72–4.11)]. Application of the exclusion criteria identified 1237 eligible TNFi first-time-user RA patients (Fig. 1) who had available data concerning RF and/or ACPA positivity. Total 674 patients had available data on both RF and ACPA; among them, 489 patients were double positive, and 75 were double negative. TNFi monotherapy was administered to 5.4% patients, and combination therapy with conventional DMARDs to 94.6%. Oral MTX was prescribed to 84.5% patients at a mean baseline dose of 8.27 mg weekly. Demographic and clinical characteristics of each group are described in Table 1. Patients with seropositivity were older and had significantly higher DAS28ESR and advanced Steinbrocker stage at treatment initiation.

Drug retention

The crude comparison of the cumulative incidence of discontinuation due to inefficacy is shown in Fig. 2. Compared with the ACPA-negative group, the ACPA-positive group exhibited significantly higher discontinuation due to insufficient response. The cumulative discontinuation rate due to insufficient response at 200 weeks was 23.0% in ACPA-positive and 13.8% in ACPA-negative patients, respectively. With respect to RF, the seropositivity had a similar tendency to higher discontinuation rate. The cumulative discontinuation rate due to ineffectiveness at 200 weeks was 19.8% in RF-positive and 16.7% in RF-negative patients, respectively.

Due to collinearity between RF and ACPA, we performed a separate multivariate analysis for each [24–26], with adjustment for the potential confounding factors. RF positivity was associated with a significantly higher risk of discontinuation due to ineffectiveness after adjustment for age, sex, DAS28ESR at baseline, Steinbrocker stage, Steinbrocker class, MTX use, and PSL use, with a hazard ratio (HR) of discontinuation of 1.73 (Table 2). ACPA positivity showed a similar tendency for higher discontinuation rates due to ineffectiveness. Another statistically significant predictor of discontinuation due to insufficient response was DAS28ESR at baseline.

DAS28ESR remission and EULAR response

DAS28ESR remission at 12 months was achieved in more RF-negative patients (46.0%) than in RF-positive (36.7%) patients ($p < 0.05$). The difference in ACPA-negative (45.5%) and ACPA-positive (39.2%) patients was not significant

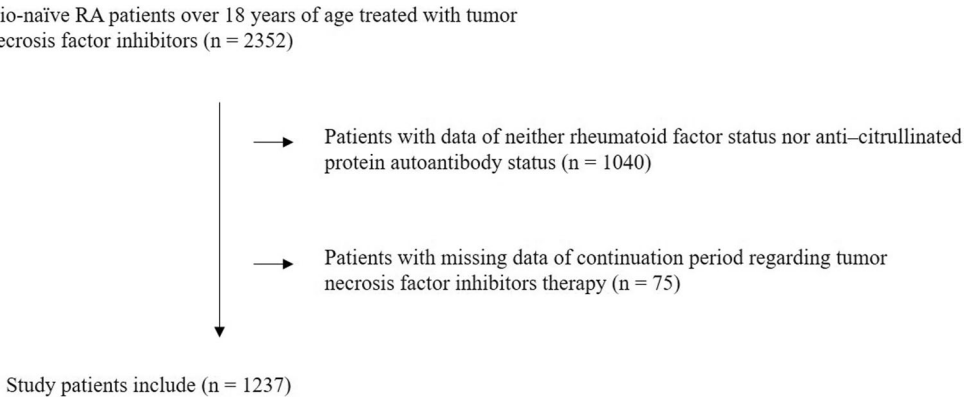

Fig. 1 Patient enrollment flow chart

($p > 0.05$). Good or moderate EULAR responses were achieved by 85.6% RF-negative and 80.5% RF-positive patients. The corresponding percentages were 83.9% and 78.6% in ACPA-negative and -positive patients (both $p > 0.05$). Multivariate logistic regression revealed an OR of 0.90 for the association of RF positivity and DAS28ESR remission and an OR of 0.63 for a good or moderate EULAR response. The ORs for ACPA were 0.93 for DAS28ESR remission and 0.51 for a good or moderate EULAR response (both $p > 0.05$).

Discussion

This study explored the association between RF and ACPA positivity and the discontinuation of TNFi therapy due to insufficient response in a cohort of RA patients from Japan. Patients who were positive for RF had higher discontinuation rates of TNFi treatment due to ineffectiveness.

Previous studies have shown contradictory results on whether the positivity of RF or ACPA are related to long-term effectiveness of TNFi therapy [9, 27–29], partly because of the differences in the definition of outcomes and statistical methods. In the present study, the Fine-Gray proportional hazard regression model was introduced. The presence of competing risks must be considered while assessing the effect of prognostic factors on the incidence of an outcome over time [22]. In our study, the cumulative incidence rate of adverse events at 200 weeks was about 14%. In this setting, the naïve use of the conventional Cox proportional hazards model that has been utilized in previous studies may lead to biased estimates of the effect of covariates [14]. Introduction of the Fine-Gray proportional hazard regression model may enhance the robustness of our results.

Table 1 Characteristics of RA patients at baseline by RF and ACPA status

	RF ($n = 1151$; 3407 patient-years)			ACPA ($n = 760$; 2285 patient-years)		
	RF positive ($n = 913$)	RF negative ($n = 238$)	p†	ACPA positive ($n = 649$)	ACPA negative ($n = 111$)	p†
Age, years (SD)	56.6 (13.5)	53.1 (14.7)	< 0.001	55.7 (13.6)	50.7 (15.7)	< 0.001
Female, no. (%)	737 (80.8)	195 (82.3)	0.64	530 (81.8)	88 (79.3)	0.51
DAS28ESR (SD)	5.28 (1.33)	4.87 (1.38)	< 0.001	5.30 (1.34)	4.78 (1.41)	< 0.001
Stage I + II/III + IV, no. (%)	312/569 (35.4/64.6)	103/120 (46.2/53.8)	0.0032	261/357 (42.2/57.8)	57/45 (55.9/44.1)	0.013
Class I + II/III + IV, no. (%)	543/338 (61.6/38.4)	174/49 (78/22)	< 0.001	434/181 (70.6/29.4)	80/22 (78.4/21.6)	0.12
Current MTX treatment, no. (%)	584 (82.7)	191 (90.1)	0.009	504 (83.2)	90 (88.2)	0.24
MTX dose, mg/week (SD)‡	8.15 (2.60)	8.56 (2.75)	0.062	8.39 (2.66)	8.93 (3.22)	0.085
Current PSL treatment, no. (%)	383 (58.1)	98 (51.0)	0.083	333 (57.8)	54 (55.1)	0.65
PSL dose, mg/day (SD)‡	5.22 (2.71)	4.96 (1.75)	0.37	5.01 (2.65)	5.45 (2.08)	0.24
BMI, kg/m^2 (SD) BMI, kg/m^2 (SD)	22.0 (3.56)	21.7 (3.79)	0.32	21.8 (3.40)	22.0 (3.90)	0.64
ADA/CZP/ETN/GLM/IFX, no. (%)	133/24/467/40/244 (14.6/2.6/51.4/4.4/26.9)	37/7/95/22/77 (15.5/2.9/39.9/9.2/32.4)	0.003	120/23/254/48/200 (18.6/3.6/39.4/7.4/31.0)	16/4/45/9/37 (14.4/3.6/40.5/8.1/33.3)	0.88

Data are presented as mean, unless otherwise stated. *SD*, standard deviation; *RA*, rheumatoid arthritis; *RF*, rheumatoid factor; *MTX*, methotrexate; *PSL*, prednisolone; *BMI*, body mass index; *ADA*, adalimumab; *CZP*, certolizumab pegol; *ETN*, etanercept; *GLM*, golimumab; *IFX*, infliximab; *ACPA*, anti-citrullinated protein antibody; *DAS28ESR*, Disease Activity Score in 28 joints calculated with erythrocyte sedimentation rate

† Chi-square test for categorical variables and *t* test for continuous variables

‡ MTX dose and PSL dose were mean values in patients with concomitant MTX and PSL treatment, respectively

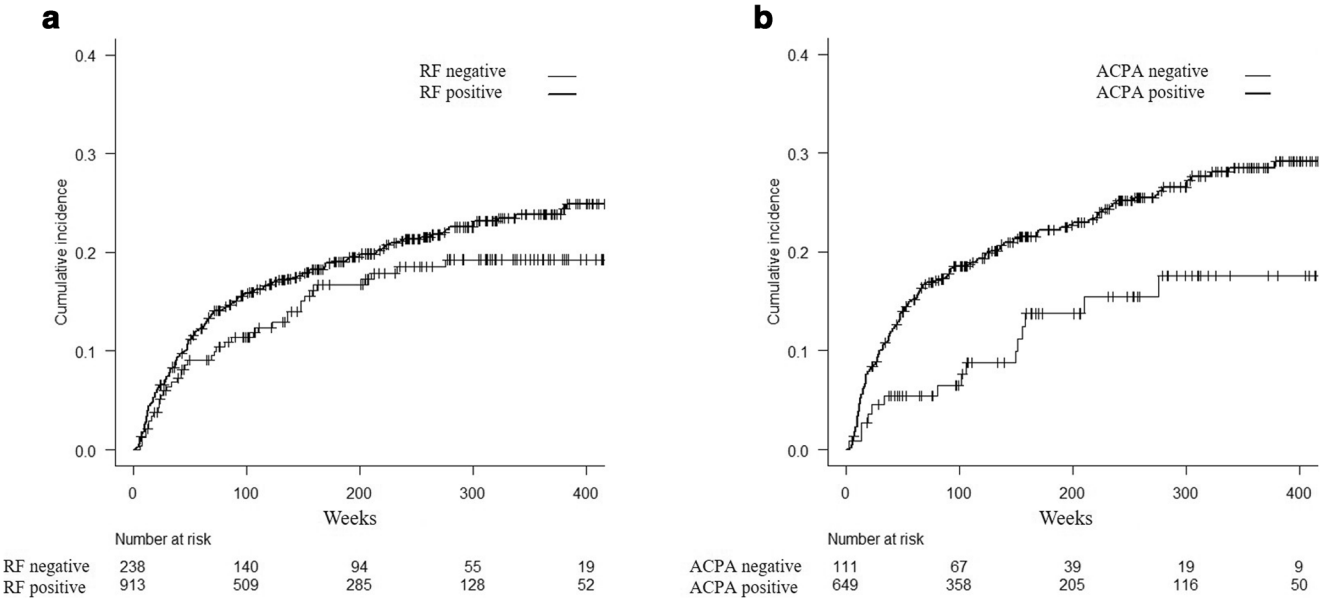

Fig. 2 Cumulative incidence of competing events and Gray test. **a** Discontinuation of tumor necrosis factor inhibitors therapy due to ineffectiveness, stratified by rheumatoid factor (RF) status ($p = 0.14$ by Gray test). **b** Discontinuation of tumor necrosis factor inhibitors therapy due to ineffectiveness, stratified by anti-citrullinated protein antibody (ACPA) status ($p < 0.05$ by Gray test)

Our result that RF positivity was related to the discontinuation of TNFi may be plausible with a biomolecular perspective. RF is of IgM isotype, while ACPA are mostly immunoglobulin G (IgG) antibodies. IgM isotype activates complement to a greater extent than IgG, consequently leading to a higher degree of inflammation. This may explain TNFi discontinuation due to insufficiency in RF-, not ACPA-positive patients.

RF positivity was inversely associated with DAS28ESR remission at 12 months, but it was not significantly associated with DAS28ESR remission or a good or moderate EULAR response of 12 months in the multivariate logistic regression analysis. The secondary endpoint results are consistent with those of the primary endpoint, but they may not strongly support the results of the primary endpoint. The discrepancy may be attributable to the differences in the statistical methods and the observation periods used to determine the primary and secondary endpoints.

The current study has certain limitations. First, we could not delineate an interaction of RF and ACPA on TNFi effectiveness because RF and anti-CCP were significantly correlated (rho = 0.50, $p < 0.001$) and few RF-negative/anti-CCP-positive or RF-negative/anti-CCP-positive patients existed. In this setting, collinearity accrued [25]; therefore, we could not assess both of RF and ACPA impacts on clinical efficacies simultaneously. Second, discontinuation of TNFi therapy was dependent on discretion of each doctor. No absolute par to judge about discontinuation of TNFi therapy existed; however, it was unlikely that the decision-makings about stopping TNFi therapy were different between seropositive and

Table 2 Fine-Gray proportional hazard regression for discontinuation of tumor necrosis factor inhibitors therapy due to ineffectiveness

Model including RF status ($n = 643$)			Model including ACPA status ($n = 524$)		
Variable	HR (95% CI)	*p*	Variable	HR (95% CI)	*p*
RF positive	1.73 (1.07–2.80)	0.023	ACPA positive	1.87 (0.92–3.80)	0.082
Age at baseline	0.98 (0.97–0.99)	0.035	Age at baseline	0.99 (0.98–1.00)	0.27
Sex (referent: male)	0.89 (0.58–1.38)	0.63	Sex (referent: male)	0.90 (0.56–1.45)	0.67
Methotrexate use	1.68 (0.96–2.96)	0.069	Methotrexate use	1.65 (0.91–2.99)	0.094
Prednisolone use	1.20 (0.83–1.75)	0.31	Prednisolone use	1.37 (0.91–2.07)	0.13
Stage III + IV (referent: I + II)	0.99 (0.98–1.01)	0.97	Stage III + IV (referent: I + II)	0.99 (0.98–1.01)	0.82
Class III + IV (referent: I + II)	1.00 (0.98–1.02)	0.67	Class III + IV (referent: I + II)	0.99 (0.98–1.01)	0.97
DAS28ESR at baseline	1.31 (1.14–1.51)	< 0.001	DAS28ESR at baseline	1.38 (1.18–1.62)	< 0.001

HR, hazard ratio; *95% CI*, 95% confidence interval; *RF*, rheumatoid factor; *ACPA*, anti-citrullinated protein antibody; *DAS28ESR*, Disease Activity Score in 28 joints calculated with erythrocyte sedimentation rate

seronegative patients. Third, information of smoking was not good enough in our study. Previous studies reported the relationships between smoking habit and seropositivity [30].

In sum, RF positivity was strongly associated with a higher discontinuation rate of TNFi therapy owing to ineffectiveness among RA patients. RF could be a helpful prognostic biomarker for the optimal use of TNFi in the treatment of RA.

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Compliance with ethical standards

Conflict of interest N.T. has received speaking fees from Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Bristol-Myers Squibb, Abbott Japan, Chugai Pharmaceutical Co. Ltd., and Pfizer Co. Ltd. N.I. has received lecture fees including service on speaker bureaus from Daiichi Sankyo Company Ltd., Takeda Pharmaceutical Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Kaken Pharmaceutical Co. Ltd., Eisai Co. Ltd., Janssen Pharmaceutical KK, Bristol-Myers Squibb, Abbott Japan, Chugai Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharmaceutical, UCB Japan, and Astellas Pharma Inc. T.K. has received lecture fees from Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Bristol-Myers Squibb, Abbott Japan, Chugai Pharmaceutical Co. Ltd., and Eisai Pharma Corporation. All other authors have declared no conflicts of interest.

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