Difficult-to-treat rheumatoid arthritis with respect to responsiveness to biologic/targeted synthetic DMARDs: a retrospective cohort study from the FIRST registry

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Abstract

Objective

Difficult-to-treat rheumatoid arthritis (dt-RA) is an emerging concept defined as persistency of signs and/or symptoms despite prior treatment. However, whether this refractoriness affects effectiveness and tolerance to next treatment is not fully understood. This study aimed to find cut-off values for a definition of dt-RA with respect to responsiveness to newly used biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs).

Methods

A retrospective cohort study was conducted using the FIRST registry. An inadequate response to current b/tsDMARDs was defined as clinical disease activity index >10 at week 22 or termination of treatment within 22 weeks due to insufficient efficacy. Cut-off values were defined according to the number of past failures to DMARDs and current dose of glucocorticoid. Responsiveness to newly used b/tsDMARDs were compared with respect to above versus below cut-off values.

Results

Failures to ≥2 conventional synthetic DMARDs (csDMARDs) and ≥4 b/tsDMARDs as well as ≥3mg/day of glucocorticoid were independent cut-off values associated with poor responsiveness to newly used b/tsDMARD treatment. Concomitant use of glucocorticoid was significantly correlated with an increased hazard of infection. Failures to ≥2 csDMARDs was associated with less improvement in inflammatory symptoms, while that to ≥4 b/tsDMARDs was associated with less improvement in health assessment questionnaire and global health as well.

Conclusion

We propose cut-off values of ≥2 failures to csDMARDs and/or ≥4 b/tsDMARDs as a definition of dt-RA with respect to responsiveness to use of b/tsDMARDs.

Key words

anti-rheumatic agents, biological products, rheumatoid arthritis, retrospective studies

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Introduction

The development of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) has revolutionarily improved the prognosis of rheumatoid arthritis (RA) patients refractory to conventional synthetic DMARDs (csDMARDs). Global evidence indicates that 30% to 60% of RA patients refractory to their first DMARD can achieve clinical remission following treatment with additional bDMARDs, and structural remission can be achieved in approximately 60% to 90% of patients treated with tumour necrosis factor inhibitors (TNFis) and methotrexate (MTX) (1). Even so, the disease remains refractory to treatment in 20% to 75% of patients on their first bDMARD (2-4) and in 40% to 55% of patients on their second bDMARD (5-8). With increasing treatment options, b/tsDMARD-refractory RA is becoming one of the most challenging areas in rheumatology. However, this type of RA is often ignored (9) and is not well-studied.

Difficult-to-treat rheumatoid arthritis (dt-RA) is an emerging concept that sheds light on such refractory status of RA. Dt-RA is operationally defined as persistency of signs and/or symptoms suggestive of inflammatory RA disease activity despite prior treatment (9). Recently, an international survey identified characteristics that are commonly recognised as those of dt-RA: persistent disease activity (disease activity score assessing 28 joints using erythrocyte sedimentation rate [DAS28-ESR] >3.2), failure to at least 2 csDMARDs and 2 b/tsDMARDs, and/or failure to tapering the glucocorticoid dose to <5–10 mg prednisone or equivalent daily for more than 1 year (10).

Although these characteristics reflect how dt-RA is experienced by physicians, cut-off values obtained by this survey is rather arbitrary (9) and there still remains a knowledge gap in how this dt-RA status predict refractoriness to next treatment. As a previous review mentioned, there is no specific biomarker or clinical marker that is able to stratify *a priori* treatment responses to specific b/tsDMARD (11). To conduct research on such predictivity, suboptimal classification may blur the precision of studies on dt-RA. Therefore, finding cut-offs that precisely predict refractoriness to next treatment is important. To find such cut-offs, cohort studies of patients treated with multiple DMARDs are essential.

The University of Occupational and Environmental Health, in Fukuoka, Japan has established a cohort of RA patients who initiated treatment with b/tsDMARDs. This cohort contains extensive data about past treatment failure of the patients. Using this cohort, this study aims to assess association of number of past treatment failures with csDMARDs and/or b/tsDMARDs and refractoriness to the next b/tsDMARD treatment. From the results of this study we propose a definition of dt-RA regarding responsiveness to a subsequent b/tsDMARD.

Patients and methods

Study setting

The FIRST registry is a multi-institutional cohort of RA patients treated with b/tsDMARDs established by the University of Occupational and Environmental Health and its affiliated hospitals.

All the patients are treated following recommendations for the management of RA treatment by the European League Against Rheumatism and Japan College of Rheumatology (12, 13). In practice, MTX, leflunomide or sulfasalazine are first treatment strategy, and if the treatment target is not achieved with at least one conventional synthetic (cs) DMARDs, then treatment with b/tsDMARD is considered. If patients cannot be treated with csDMARDs due to some reasons such as renal dysfunction, then treatment with a biological DMARD is considered as the first choice of the treatment.

The registry has accumulated data from patients who started b/tsDMARDs since the first agent, infliximab (IFX), was approved in Japan in 2003. Until June 2019, 3,535 patients have been enrolled in this registry. Treatments have included five TNFis (IFX, etanercept [ETA], adalimumab [ADA], golimumab [GLM], and certolizumab [CZP]), an anti–interleukin-6 receptor antibody (tocilizumab; TCZ), a cytotoxic T-lymphocyte–associated antigen-4 immunoglobulin (abatacept; ABT), and a Janus

kinase inhibitor (tofacitinib; TOF). Rituximab is not approved as a treatment option for RA in Japan.

At the start of b/tsDMARD treatment, baseline data are collected, including demographics (age, gender, height, weight), disease characteristics (disease duration, titres of anti-cyclic citrullinated protein [CCP] antibody), measures of disease activity (swollen joint count [SJC] and tender joint count [TJC], patient's visual analogue scale [VAS], doctor's VAS, patient global assessment [GH], titres of erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), functional status (class, stage, Health Assessment Questionnaire [HAQ] score), and treatment (current dose of glucocorticoid and MTX, previous and current use of csDMARDs and b/tsDMARDs). Follow-up data on disease activity are collected at 2, 22, 54 weeks, and then yearly after the start of the therapy. If treatment is discontinued, the date of and reason for discontinuation are also recorded.

Patient selection and data collection

– Eligibility criteria

Patients who were enrolled in the FIRST registry from 2003 to June 2019 were included. Collected data included demographics, disease characteristics, measures of disease activity, present and past treatment at the start of treatment, and disease activity data 22 weeks after treatment. If a treatment was discontinued within 22 weeks due to infection, other adverse events, or lack of response to treatment, the date of and reason for discontinuation were also collected. Each b/tsDMARD episodes of the same patient was treated as an independent episode.

– Exclusion criteria

Data were excluded when a treatment was discontinued within 22 weeks from reasons other than infection, adverse events, lack of response, or remission. Among those who continued the treatment, those whose CDAI at week 22 were not available were also excluded.

– Definition of inadequate response

The inadequate response to current b/tsDMARD (current b/tsDMARD-IR) group consisted of patients with moderate-to-high disease activity (clinical disease activity index [CDAI] >10) at week 22 and those who stopped treatment within 22 weeks due to insufficient efficacy. The control group included patients who achieved remission or low disease activity (CDAI ≤10) at week 22 and those who stopped treatment within 22 weeks due to remission. We used CDAI instead of DAS28-ESR for assessment of disease activity because CRP and ESR titres would be more strongly affected by TCZ usage than other b/tsDMARDs.

Patients who were treated with more the one classes of b/tsDMARDs were categorised as class-switch (+). Others who were treated with only TNFis or those who were treated with b/tsDMARDs for the first time (b/tsDMARD naïve) were categorised as class-switch (-).

Statistical analysis

For continuous variables, Wilcoxon's rank sum test was used to compare the two groups. To minimise the effects of outliers, robust method was applied for the following regression tests. Missing data were imputed by estimated values based on other variables used in the multiple regression.

For sensitivity analysis, each variable was converted into a categorical variable in which the numbers of samples included in each category become as equal as possible. Differences between groups were assessed using the chi-squared test, and regression analyses were also conducted using these categorical variables with non-imputed data.

– Assessment of cut-offs for the components of the dt-RA

Components of the condition of dt-RA were categorised into three groups based on previous reports (9,14): past failure to csDMARDs, past failure to b/tsDMARDs, and current use of glucocorticoids. For past failure to DMARDs, four cut-off values were defined according to the number of failures: ≥1, ≥2, ≥3, and ≥4 failures. In addition, past failure specifically to MTX was also assessed as a cut-off. For current use of glucocorticoids, five cut-off values were defined according to prednisolone equivalent dose of glucocorticoid: ≥1 mg/day, ≥3 mg/day, ≥5 mg/day, ≥7.5 mg/day, and ≥10 mg/ day.

To determine differences between patients in the b/tsDMARD-IR and control groups, mixed-effect logistic regression models were used to compare above *versus* below cut-off values. The mixed-effect regression model was fitted with age, gender, body mass index (BMI), disease duration, with or without class-switch of the treatment, anti-CCP antibody positivity, MTX dose, past failures to MTX, CDAI at week 0, and glucocorticoid use at week 0 as fixed effects and drug types as random effects. Fixed effects also included number of past failures to b/tsDMARDs and glucocorticoid dose for analysis of csDMARD failures, number of past failures to csDMARDs and glucocorticoid dose for analysis of b/tsDMARD failures, and numbers of past failures to cs- and b/tsDMARDs for analysis of glucocorticoid use.

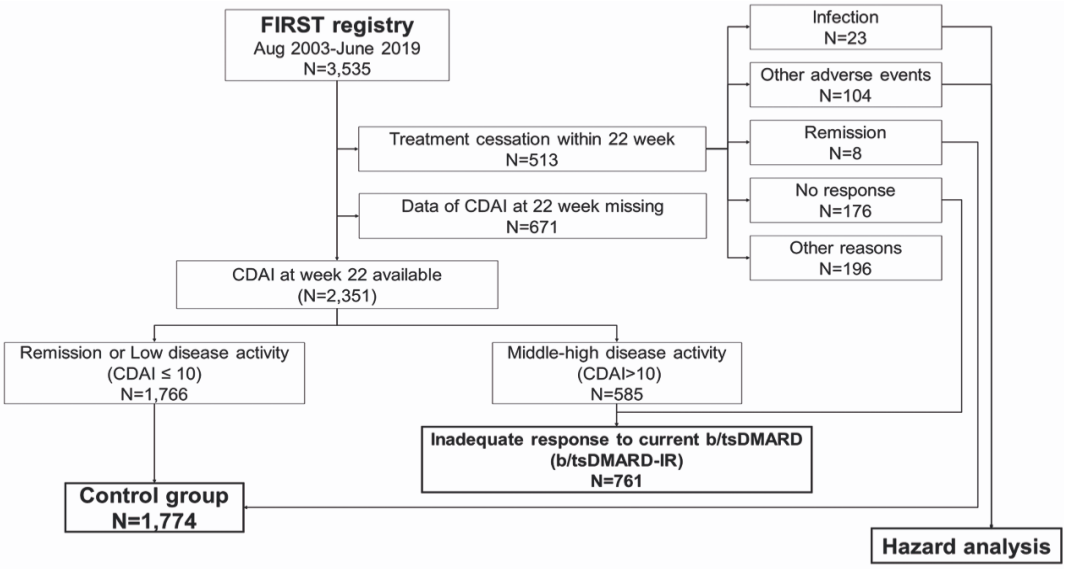
In studies with very few outcomes, multivariate logistic regression analysis tends to overfit the data, resulting in biased estimation. Therefore, an inverse-probability score-based weighted (IPW) method was performed using a logistic regression model to adjust for any potential confounders. Variables that showed significant correlation with numbers of past failures to DMARDs were included as covariates.

– Analyses of clinical indicators associated with refractoriness

Clinical indicators are expected to improve during the observational period (22 weeks) after treatment initiation. Therefore, change in clinical indicators from week 0 to week 22 (Δvalues) can be used as substitutes for indicators of treatment effectiveness. For these indicators, negative Δvalues indicate the treatment was less effective. To compare treatment effectiveness between two groups, the Δvalue was calculated by subtracting the value at week 22 from that at week 0.

The Δvalues were used in mixed-effect regression analysis to assess correlations between cut-off values and these clinical indicator substitutes. The same covariates as those used in the mixed-effect logistic regression analysis described above were used.

Fig. 1. Patient selection



– Assessment of adverse event incidence

To compare hazards of adverse events with respect to above *versus* below cut-off values, a Cox proportional hazards regression model was used. In addition, Nelson-Aalen cumulative hazard estimation was shown graphically. For all methods, a *p*-value <0.05 was considered statistically significant.

Ethical approval and consent to participate

The institutional review board of the University of Occupation and Environmental Health approved the study (approval code: 04-23). Informed consent was obtained from all participants of the FIRST study.

Results

Baseline factors affecting the current b/tsDMARDs-IR group at week 22

Among 3,535 registered patients, treatment was discontinued in 513 patients, 23 of whom stopped treatment due to infection, 104 due to other adverse events, 8 due to remission, 176 due to lack of response, and 196 due to other reasons such as economic reasons. Among the remaining 3,022 patients, CDAI data at week 22 were missing for 671 patients. Of the remaining 2,351 patients, 1,766 achieved remission or low disease activity (CDAI ≤10) and 585 showed moderate-to-high disease activity (CDAI >10) at week 22. In total, 761 patients (77,507 patient-days) were classified into the current b/tsDMARDs-IR group and 1,774 (133,056 patient-days) into the control group (Fig. 1).

The backgrounds of patients in the current b/tsDMARDs-IR and control groups are shown in Table I. As Shapiro-Wilk testing rejected a normal distribution for all of the continuous variables listed in Table I, the two groups were compared using Wilcoxon rank-sum testing. Each continuous variables were also converted into categorical variables and compared by chi-squared testing. Patients in the b/tsDMARDs-IR group had a longer disease duration, higher disease activity, higher CRP titres, a lower rate of anti-CCP antibody positivity but higher average titre, lower MTX doses at week 0, and higher frequency in failures to csDMARDs, higher frequency in the current use of mizoribine and tacrolimus compared with patients in the control group. Types of newly used b/tsDMARDs differed between groups. However, no significant difference in previously used b/tsDMARD types and experience in class-switch was observed.

Cut-offs for the current b/tsDMARDs-IR group at week 22

Next, mixed-effect logistic regression analyses were performed for each cut-off value. For csDMARDs, the cut-off values associated with a significant difference in responsiveness to b/tsDMARD treatment were ≥2 failures to the treatment. Past failure to MTX treatment also significantly associated with the increase in the responsiveness. For b/tsDMARDs, the cut-off value was ≥4 failures (Table II).

Another definition of dt-RA that has gained global consensus is the inability to reduce glucocorticoid use. Due to limited available data, we used glucocorticoid dose at week 0 (mg/day, prednisolone equivalent) as a substitute for previous use of glucocorticoids. Use of ≥3mg/day of glucocorticoid were associated with refractoriness to a b/tsDMARD (Table II).

As the number of patients who experienced ≥4 failures to b/tsDMARD treatment was small (n=48), this difference might have been caused by confounders such as disease duration. Indeed, logistic regression revealed significant differences in gender, age, BMI, disease duration, CDAI and ESR titres at week 0, anti-CCP antibody positivity, glucocorticoid dose, and MTX dose between patients with ≥4 failures to b/tsDMARDs and those with ≤3 failures (data not shown). Therefore, adjustment for these confounders was performed using IPW, and the average effect of each cut-off value was calculated. Even after this adjustment, ≥2 failures to csDMARDs and ≥4 failures to b/tsDMARDs but not past failure to MTX appeared to be independent cut-offs. These data indicate that refractoriness to ≥2 previous csDMARDs and/or ≥4 previous b/tsDMARDs could be defined

Table I. Patient background characteristics at week 0.
Chi-squared test (p1) and Wilcoxon's rank sum test (p2) were used to compare categorical and continuous variables, respectively.

		b/tsDMARD-IR (n=761)				Control (n=1,774)					
		n	%	Mean ± SD	Median	n	%	Mean ± SD	Median	p1	p2
Gender	Female	641	84.2	NA		1,451	81.8	NA		NA	0.14
	Male	120	15.8			323	18.2				
Age (year)	<50	130	17.1	61.7 ± 13.4	63	373	21.0	60.1 ± 14.6	62	0.03	0.03
	50-59	186	24.4			374	21.1				
	60-69	201	26.4			519	29.3				
	70-79	194	25.5			402	22.7				
	≥80	50	6.6			106	6.0				
Disease duration (months)	<12	102	13.4	106.7 ± 116.4	62	253	14.3	93.7 ± 110.1	48	<0.01	0.08
	12-24	76	10.0			222	12.5				
	24-60	201	26.4			503	28.4				
	60-120	142	18.7			320	18.0				
	>120	240	31.5			474	26.7				
CDAI	Low (<10)	19	2.5	31.3 ± 13.5	30	185	10.4	23.4 ± 12.2	21.4	<0.01	<0.01
	Middle (10-22)	166	21.8			669	37.7				
	High (>22)	468	61.5			758	42.7				
	Missing	108	14.2			162	9.1				
DAS28-CRP	Low (<2.7)	13	1.7	5.3 ± 1.2	5.29	111	6.3	4.6 ± 1.3	4.52	<0.01	<0.01
	Middle (2.7-4.1)	110	14.5			538	30.3				
	High (>4.1)	638	83.8			1,125	63.4				
DAS28-ESR	Low (<3.2)	14	1.8	6.1 ± 1.3	6.11	93	5.2	5.3 ± 1.3	5.305	<0.01	<0.01
	Middle (3.2-5.1)	163	21.4			683	38.5				
	High (>5.1)	583	76.6			996	56.1				
	Missing	1	0.1			2	0.1				
CRP (mg/dL)	<0.3	200	26.3	2.9 ± 3.7	1.41	537	30.3	2.2 ± 3.2	0.895	<0.01	<0.01
	0.3-1	125	16.4			385	21.7				
	1.01-3	177	23.3			427	24.1				
	3.01-10	209	27.5			355	20.0				
	>10	50	6.6			70	3.9				
ESR (mm/1hour)	<25	178	23.4	55.5 ± 33.6	52	494	27.8	49.7 ± 31.5	46	<0.01	<0.01
	25-49	193	25.4			480	27.1				
	50-74	158	20.8			386	21.8				
	≥75	232	30.5			414	23.3				
anti-CCP antibody (IU/mL)	Negative (≤ 4.5)	164	21.6	288.0 ± 726.7	65.3	359	20.2	257.7 ± 524.8	77.9	0.23	0.02
	Positive (> 4.5)	425	55.8			1,200	67.6				
	Missing	172	22.6			215	12.1				
Dose of GC (mg / day, prednisolone equivalent)	0	521	68.5	1.5 ± 2.7	0	1,394	78.6	1.5 ± 5.3	0	<0.01	<0.01
	1-3	77	10.1			120	6.8				
	3.1-5	104	13.7			158	8.9				
	5.1-7.5	29	3.8			36	2.0				
	7.6-10	25	3.3			27	1.5				
	>10	5	0.7			39	2.2				
Dose of MTX (mg/week)	0	203	26.7	8.0 ± 5.8	8	371	20.9	9.4 ± 5.8	10	<0.01	<0.01
	2-6	80	10.5			117	6.6				
	7-9	135	17.7			278	15.7				
	10-14	207	27.2			541	30.5				
	≥15	136	17.9			467	26.3				
Number of csDMARD failure	0	3	0.4	2.4 ± 1.4	2	20	1.1	2.2 ± 1.3	2	<0.01	0.09
	1	170	22.3			399	22.5				
	2	191	25.1			420	23.7				
	3	126	16.6			238	13.4				
	≥4	20	2.6			28	1.6				
	Missing	251	33.0			669	37.7				
Number of b/tsDMARD failure	0	466	61.2	0.6 ± 1.0	0	1,090	61.4	0.6 ± 0.9	0	0.67	0.13
	1	176	23.1			436	24.6				
	2	70	9.2			151	8.5				
	3	25	3.3			68	3.8				
	≥4	24	3.2			29	1.6				

		b/tsDMARD-IR (n=761)				Control (n=1,774)					
		n	%	Mean ± SD	Median	n	%	Mean ± SD	Median	p1	p2
Current use of b/tsDMARD	IFX	140	18.4	NA		264	14.9	NA	NA		0.03
	ETA	100	13.1	NA		223	12.6	NA	NA		0.69
	ADA	84	11.0	NA		353	19.9	NA	NA		<0.01
	GLM	38	5.0	NA		53	3.0	NA	NA		0.01
	CZP	63	8.3	NA		153	8.6	NA	NA		0.78
	TCZ	153	20.1	NA		313	17.6	NA	NA		0.14
	ABT	158	20.8	NA		326	18.4	NA	NA		0.16
	TOF	25	3.3	NA		89	5.0	NA	NA		0.05
Class switch	Yes	163	21.4	NA		410	23.1	NA	NA		0.35
Past use of b/tsDMARD	IFX	119	15.6	NA		271	15.3	NA	NA		0.81
	ETA	30	3.9	NA		49	2.8	NA	NA		0.12
	ADA	67	8.8	NA		135	7.6	NA	NA		0.31
	GLM	26	3.4	NA		52	2.9	NA	NA		0.51
	CZP	7	0.9	NA		18	1.0	NA	NA		0.83
	TCZ	61	8.0	NA		123	6.9	NA	NA		0.34
	ABT	49	6.4	NA		117	6.6	NA	NA		0.88
	TOF	6	0.8	NA		16	0.9	NA	NA		0.78
Current use of csDMARD other than MTX	CyA	0	0.0	NA		5	0.3	NA	NA		0.14
	DPC	1	0.1	NA		2	0.1	NA	NA		0.90
	IGU	9	1.2	NA		17	1.0	NA	NA		0.61
	Lef	9	1.2	NA		21	1.2	NA	NA		1.00
	Mz	5	0.7	NA		0	0.0	NA	NA		0.01
	SASP	50	6.6	NA		106	6.0	NA	NA		0.57
	Tac	82	10.8	NA		145	8.2	NA	NA		0.04
Past use of csDMARD	Act	43	5.7	NA		28	1.6	NA	NA		<0.01
	Buc	169	22.2	NA		299	16.9	NA	NA		<0.01
	CyA	26	3.4	NA		33	1.9	NA	NA		0.02
	DPC	36	4.7	NA		36	2.0	NA	NA		<0.01
	Gold	48	6.3	NA		62	3.5	NA	NA		<0.01
	IGU	25	3.3	NA		49	2.8	NA	NA		0.47
	IVCY	9	1.2	NA		9	0.5	NA	NA		0.06
	Lef	39	5.1	NA		65	3.7	NA	NA		0.09
	MTX	158	20.8	NA		267	15.1	NA	NA		<0.01
	Mz	37	4.9	NA		35	2.0	NA	NA		<0.01
	SASP	256	33.6	NA		507	28.6	NA	NA		0.01
	Tac	140	18.4	NA		227	12.8	NA	NA		0.01

SD: standard deviation; NA: not applicable; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; MTX: methotrexate; b/tsDMARDs: biological or targeted synthetic DMARDs; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CCP: cyclic citrullinated peptide, GC: glucocorticoid; IFX: infliximab; ETA: etanercept; ADA: adalimumab; GLM: golimumab; CZP: certolizumab pegol; TCZ: tocilizumab; ABT: abatacept; TOF: tofacitinib; CYA: cyclosporine; DPC: d-penicillamine; IGU: iguratimod; LEF: leflunomide; MZ: mizoribine; SASP: salazosulphapyridine; Tac: tacrolimus; ACT: actarit; BUC: bucillamine; IVCY: intravenous cyclophosphamide.

as cut-off values for dt-RA regarding responsiveness to another b/tsDMARD (Table II). Significant association was also observed in ≥3mg/day of glucocorticoid, suggesting the use of low dose of glucocorticoid as a risk factor of the refractoriness.

Clinical and laboratory findings associated with the identified cut-off values for refractoriness to previous treatments

To determine the major factors affected by the identified cut-offs, a mixed-effect multiple regression model analysis and IPW were conducted using Δvalues of the variables associated with disease activity. The factors that were affected by each cut-off appear to be slightly different. Refractoriness to ≥2 previous csDMARDs was significantly associated with less improvement in the number of swollen joints, patient's VAS, doctor's VAS, CRP titre, ESR titre, and GH, while refractoriness to ≥4 previous b/tsDMARDs was associated with less improvement in HAQ as well. However, only ESR titre showed significant association in IPW (Table III). Use of ≥3mg/day of glucocorticoid was significantly associated with less improvement in patient's VAS, CRP, and GH in both multiple regression and IPW.

Sensitivity analyses

Sensitivity analysis was conducted using data in which the missing data was not imputed. These analyses also showed that ≥2 failures to csDMARDs, ≥4 failures of b/tsDMARDs, and ≥3 mg/day of glucocorticoid use as the cut-off value of the next treatment with b/tsDMARDs (data not shown).

Analyses on clinical and laboratory factors showed that refractoriness to ≥2 previous csDMARDs was significantly associated with less improvement in ESR titre and GH, while refractoriness to ≥4 previous b/tsDMARDs was associated with less improvement in HAQ and GH (data not shown).

Cut-offs for adverse events

Treatment failure due to adverse events is often included in the definition of dt-RA(14). To determine whether numbers of treatment failures and glu-

Table II. Analysis of thresholds of refractoriness to current b/tsDMARDs.
Odds ratios and average effects of inadequate response to current b/tsDMARD treatment (current b/tsDMARD-IR) were calculated using mixed-effect logistic regression and inverse-probability score-based weighted methods (IPW), respectively.

		b/tsDMARD-IR		Control		Mixed-effect logistic regression				IPTW			
		n	%	n	%	OR	95% CI		*p*	Average effect	95% CI		*p*
Number of csDMARD failure	≥1 (n=2,453)	732	29.8	1.721	70.2	0.82	0.41	1.62	0.57		NA†		
	≥2 (n=1,228)	414	33.7	814	66.3	1.51	1.28	1.78	<0.01	0.05	0.01	0.09	0.01
	≥3 (n=618)	223	36.1	394	63.9	1.40	0.95	2.05	0.09	0.04	0.00	0.09	0.03
	≥4 (n=253)	97	38.3	156	61.7	1.43	0.76	2.69	0.27	0.05	0.00	0.11	0.07
Number of b/tsDMARD failure	≥1 (n=979)	295	30.1	684	69.9	1.10	0.94	1.30	0.23	0.04	0.00	0.08	0.08
	≥2 (n=367)	119	32.4	248	67.6	1.13	0.86	1.49	0.37	0.04	-0.02	0.09	0.20
	≥3 (n=146)	49	33.6	97	66.4	1.03	0.69	1.55	0.88	0.04	-0.04	0.12	0.31
	≥4 (n=48)	24	45.3	29	54.7	1.71	1.14	2.57	0.01	0.13	0.00	0.25	0.05
History of MTX failure	(n=425)	158	37.2	267	62.8	1.37	1.14	1.65	<0.01	0.02	-0.04	0.08	0.55
Dose of GC at week 0 (mg/day, prednisolone equivalent)	≥1 (n=620)	240	38.7	380	61.3	1.41	1.01	1.97	0.04	0.04	-0.01	0.09	0.11
	≥3 (n=423)	163	38.5	260	61.5	1.36	1.02	1.82	0.04	0.07	0.00	0.13	0.04
	≥5 (n=321)	115	35.8	206	64.2	1.10	0.77	1.59	0.60	0.02	-0.05	0.09	0.60
	≥7.5 (n=140)	48	34.3	92	65.7	0.86	0.51	1.42	0.55	-0.06	-0.15	0.04	0.24
	≥10 (n=88)	25	28.4	63	71.6	0.75	0.42	1.33	0.33	-0.04	-0.17	0.09	0.52

csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; b/tsDMARDs: biological or targeted synthetic DMARDs; GC: glucocorticoid; OR: odds ratio; CI: confidence interval; AE: average effect; NA: not applicable. †Sample size (number of no csDMARD failure) was too small to calculate.

cocorticoid dose affect the probability of adverse events, hazards of adverse events were compared above *versus* below cut-offs.

In total, 23 cases (1,661 patient-days) of infection and 104 cases (7,454 patient-days) of other adverse events that led to treatment cessation within 22 weeks were identified. The same variables as in Tables II and III were used for adjustment of the Cox proportional hazards analysis. The analyses revealed that use of any dose of glucocorticoids were significantly correlated with an increased hazard ratio (HR) of infection that led to treatment cessation (Fig. 2). Failures to ≥3csDMARDs appeared to weakly correlate with the adverse event, but not statistically significant. No significant association between the HR of infection and number of failures to b/tsDMARDs was observed. Also there was no significant association between other adverse events within 22 weeks and past treatment failures was observed (Fig. 3). Past failure to MTX showed no association with neither infection nor other adverse events (data not shown).

Discussion

This is the first study to identify cut-offs of dt-RA status that predict effectiveness and tolerance to the next b/tsDMARD. Based on the results of this study, we propose a definition of dt-RA to be failure to ≥2 csDMARDs and/or ≥4 b/tsDMARDs, because these cut-offs predict inadequate response to the next b/tsDMARD.

One of the major challenges in RA treatment is predictability of the treatment. Current recommended treatment approach in the management of RA is based on 'heuristic' decisions, on 'trial and error' basis (15), and precision medicine remains one of the major unmet needs in the management of RA. The cut-offs identified in this research may make it possible to adequately categorise dt-RA, which is essential for further studies that elucidate risk factors and molecular markers to predict the refractory status of RA.

Refractoriness to a b/tsDMARDs is caused by a variety of mechanisms. Incorrect targeting is supported by studies that compared non-TNF-targeted bDMARDs, and TNFis as second bDMARDs for patients with insufficient response to a first TNFi (16,17). For patients who received treatment with incorrect targeting, the probability of effectiveness of the next b/tsDMARD does not differ from that of the first treatment. This may explain the present result that no significant difference was observed between patients who failed ≥1, ≥2, and ≥3 b/tsDMARDs and the efficacy of the next b/tsDMARDs treatment (Table II).

In contrast, multi-b/tsDMARD refractoriness may occur via different mechanisms. One possible explanation is induction of anti-drug antibodies (ADAbs), which is more commonly observed among patients treated with TNFis than with other agents (18). Analysis in Table II showed that history of MTX, an anchor drug that reduce ADAbs production, weakly related to the b/tsDMARD-IR status, which support the idea. However, previous study showed that patients who previously developed ADAbs against a TNFi are reported to be more likely to develop additional ADAbs with subsequent TNFi treatment (19, 20). As there was no significant difference in between class-switch and within-class treatment change between b/tsDMARDs-IR and control groups (Table I), ADAbs production was not fully explain the mechanism of this refractoriness. In addition, the presence of ADAbs is associated with drug safety and tolerability as well as refractoriness (20), but no associations between cut-off values and the frequency of adverse events were observed in the present study (Fig. 3). Further analyses are required to study the characteristics of patients with ≥4 failures to b/tsDMARDs.

Table III. Analysis of factors affected by treatment failure to DMARDs.
Δvalue (value at week 0 – value at week 22) was compared between above- and below- cut-off values for variables associated with disease activity using mixed-effect regression and inverse-probability score-based weighted methods (IPW), respectively.

		Mixed-effect regression				IPW			
		Average Δvalue	95% C.I.		*p*	Average effect	95% CI		*p*
Treatment failure to ≥2 csDMARDs	TJC	0.58	-0.95	2.10	0.46	0.57	-0.12	1.26	0.10
	SJC	-0.28	-0.30	-0.26	<0.01	-0.08	-0.57	0.40	0.74
	Pt-VAS	-1.91	-2.37	-1.45	<0.01	0.09	-2.78	2.97	0.95
	Dr-VAS	-2.65	-3.32	-1.97	<0.01	-1.66	-3.78	0.46	0.12
	CRP (mg/dL)	-0.23	-0.40	-0.05	0.01	-0.07	-0.19	0.06	0.29
	ESR (mm/1h)	-3.88	-5.10	-2.67	<0.01	-3.35	-6.08	-0.62	0.02
	HAQ	-0.01	-0.04	0.01	0.32	0.01	-0.05	0.08	0.71
	GH (mm)	-3.50	-4.88	-2.13	<0.01	-1.49	-4.22	1.24	0.29
Treatment failure to ≥4 bDMARDs	TJC	-0.15	-2.76	2.47	0.91	-1.24	-3.52	1.03	0.28
	SJC	-0.57	-1.10	-0.04	0.03	-0.70	-2.52	1.13	0.46
	Pt-VAS	-5.93	-11.03	-0.83	0.02	-5.59	-13.07	1.88	0.14
	Dr-VAS	-4.14	-5.90	-2.37	<0.01	-3.01	-8.24	2.22	0.26
	CRP (mg/dL)	-0.60	-0.86	-0.35	<0.01	-0.02	-0.65	0.62	0.96
	ESR (mm/1h)	-6.07	-6.95	-5.19	<0.01	-9.98	-15.59	-4.37	<0.01
	HAQ	-0.16	-0.30	-0.03	0.02	-0.12	-0.33	0.09	0.26
	GH (mm)	-11.86	-18.21	-5.51	<0.01	-9.05	-18.04	-0.06	0.05
≥3mg/day of glucocorticoid use at week 0	TJC	-1.21	-2.34	-0.08	0.04	-1.08	-1.94	-0.21	0.02
	SJC	0.40	-0.10	0.90	0.11	0.22	-0.42	0.86	0.50
	Pt-VAS	-5.98	-8.49	-3.47	<0.01	-7.14	-10.76	-3.52	<0.01
	Dr-VAS	-2.20	-2.30	-2.10	<0.01	-2.86	-5.77	0.05	0.05
	CRP (mg/dL)	0.49	0.37	0.61	<0.01	-0.25	-0.46	-0.03	0.02
	ESR (mm/1h)	-0.51	-6.28	5.27	0.86	-3.12	-6.52	0.28	0.07
	HAQ	-0.03	-0.13	0.08	0.64	-0.07	-0.15	0.01	0.11
	GH (mm)	-3.31	-10.87	4.26	0.39	-4.18	-7.64	-0.72	0.02

csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; b/tsDMARDs: biological or targeted synthetic DMARDs; TJC: tender joint count; SJC: swollen joint count; Pt-VAS: patients-visual assessment score; Dr-VAS: doctor-visual assessment score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; GH: global health assessment; CI: confidence interval.

Another reason for inadequate response to b/tsDMARD could be "false refractoriness," which is characterised by persistent symptoms despite lack of inflammation (21). One cause of false refractoriness is increased comorbidity burden, which has been reported to lower response rate and retention rate of bDMARDs (22). The present finding that treatment failure to ≥4 b/tsDMARDs was associated with HAQ both in mixed-effect regression and in sensitivity analysis. This suggests that resistance to multiple b/tsDMARDs might be caused by increased comorbidity burden. However, GH and ESR titre were also significantly correlated with refractoriness, which cannot be explained by the "false refractoriness" concept. Therefore, there might be several different mechanisms of refractoriness among patients who were refractory to multiple b/tsDMARDs.

The cut-off of ≥4 b/tsDMARDs may look incompatible to the previous reports that defines dt-RA as those who are refractory to ≥2 csDMARDs and ≥2 b/tsDMARDs (10, 14). This might be because we studied treatment failure to csDMARDs and that to b/tsDMARDs independently. In addition, this study focused only on the responsiveness to the next b/tsDMARD and not overall refractoriness nor progression of the disease. Therefore, our result does not contradict previous reports.

A previous study showed that two or more failures to csDMARDs were correlated with comorbidity burden in RA patients (23). As some comorbidities, such as interstitial lung disease, also increase the risk of infection, the weak correlation between ≥3 failures to csDMARDs and a higher hazard of infection (Fig. 2) may be due to the comorbidities in patients who have experienced multiple failures to csDMARDs.

In an international survey, many rheumatologists mentioned characteristics other than joint symptoms as factors contributing to dt-RA, including extra-articular manifestations, comorbidities, side effects, and treatment non-adherence. The current study did not show a significant difference in the hazards of adverse events other than infection. However, based on the appearance of the cumulative hazard estimate graphs (Fig. 2-3), this absence of a significant association might be due to the sample size being too small. In addition, this study could not assess extra-articular manifestations and comorbidities due to lack of precise information.

A global consensus about the definition of dt-RA regarding use of glucocorticoids is failure to taper glucocorticoids to <5–10 mg prednisone or equivalent daily (14). The present study showed that treatment with glucocorticoids was associated with responsiveness to b/tsDMARDs as well as hazard of severe infection that leads to treatment cessation. This result underlines the importance of using minimum doses of glucocorticoids, while considering the benefit of their use (24-26).

Our study is limited primarily by its in-

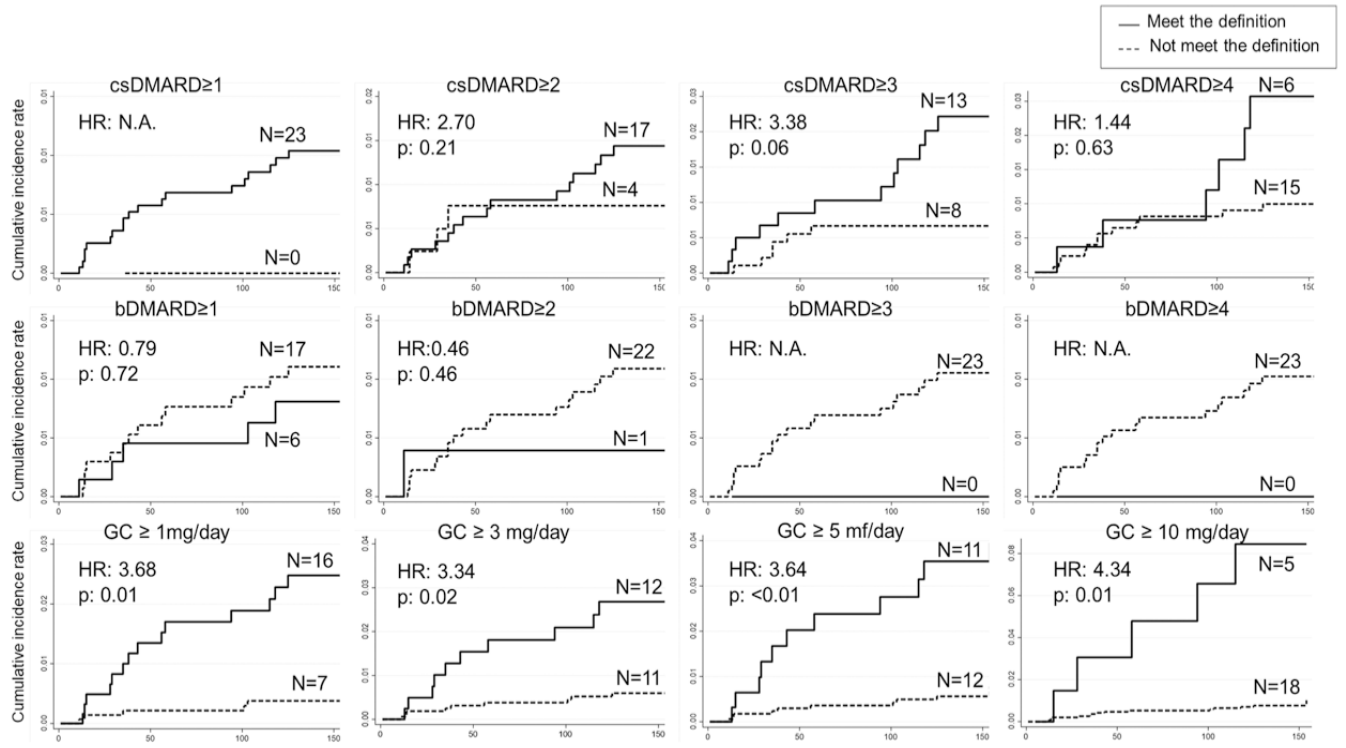


Fig. 2. Cumulative hazard of treatment cessation due to infection within 22 weeks (23 cases, 1,661 patient-days).

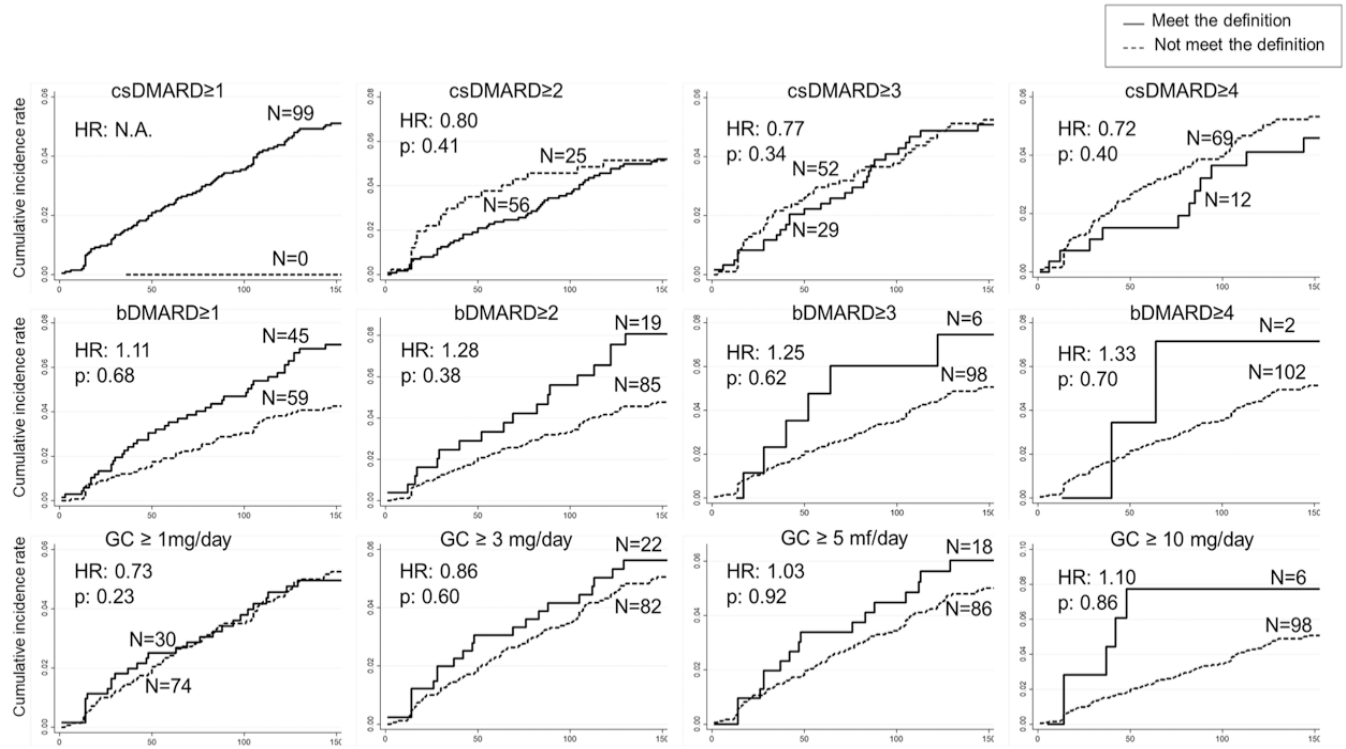


Fig. 3. Cumulative hazard of treatment cessation due to other adverse events within 22 weeks (104 cases, 7,454 patient-days).

herently retrospective nature. In particular, there are several limitations related to data collection. Firstly, this registry included several episodes of the same patients who received different agents, because if all duplicates are excluded, the number of responders would be too small. Secondly, as aforementioned, comorbidity data, such as chronic kidney disease and interstitial pneumonia, were not included, which could confound the outcomes. Thirdly, almost all the patients included in this study are Japanese with Asian ethnicity and a relatively small body size, among whom the

risks of adverse events may be different from people of different ethnic or demographic backgrounds. Nevertheless, it is not clear whether this limitation substantially impact the cut-off values we have proposed.

Another limitation is that the number of patients varied by agent type. Although the mixed-effect model was applied to adjust for this difference, such methodology may not fully adjust for all confounders related to choices of treatments. In addition, the number of patients included in certain categories, such as ≥4 failures to b/tsDMARDs, was very small. Therefore, based on the Cox regression model illustrated in Figures 2 and 3, we cannot determine whether the absence of significant statistical difference indicates no difference or whether the sample size was too small to show a difference.

Finally, there is a limitation in the validity of our findings outside of Japan because treatment options are slightly different from those in other countries. For example, in Japan rituximab has not been approved as treatment of RA, thus this agent was not included as treatment option. Newly developed b/tsDMARDs such as belimumab and upadacitinib were not included, either. Therefore, cut-off values of b/tsDMARDs may be different in countries in which rituximab and other b/tsDMARDs are approved. In addition, use of csDMARDs may also be different. For example, several csDMARDs used in this study such as bucillamine and mizoribine. On the contrary, use of leflunomide is not so common in Japan due to the history of lethal severe adverse events soon after its launch (27, 28). Even with these limitations, our study is important in that it first showed cut-off values of responsiveness to treatment based on cohort study.

In conclusion, this study assessed cut-off values that predict refractoriness to the next b/tsDMARD treatment. Our results suggest that cut-offs of ≥2 failures to csDMARDs and/or ≥4 b/tsDMARDs are independent predictors. We propose these cut-offs as a definition of dt-RA, which can be used for further research for better understanding of dt-RA status, and for precision medicine in RA.

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