"treat-to-target (T2T)" [3] has emerged, which defines clinical remission as the goal of treatment and seeks to educate the many people involved in treating RA that tight control is the cornerstone of treatment. Then, in 2011, new criteria aiming for even higher levels of remission than those defined by the ACR and EULAR—the simplified disease activity index (SDAI), the clinical disease activity index (CDAI), and the Boolean definition—were proposed [4]. As a consequence of all this, the aim is for RA to be diagnosed sooner, and the goal of treatment is to meet the new remission criteria.

Tocilizumab (TCZ), developed in Japan, is the first anti-interleukin-6 (IL-6) receptor monoclonal antibody that targets IL-6. TCZ, which can now be used in the USA in patients who have shown inadequate response to anti-tumor necrosis factor (TNF) agents, can also be used in Japan as a first-line biologic treatment, and is applicable to some 30 % of patients in the clinical setting [5–7].

Using data from the Tsurumai Biologics Communication (TBC) Registry (a database of patients treated with biologics in the Department of Orthopedics in the Faculty of Medicine at Nagoya University and 20 affiliated institutions), we carried out an investigation to confirm the therapeutic response to TCZ, and we then considered its efficacy when used according to the ACR and EULAR recommendations and the T2T concept; we also examined the remission status achieved with the drug as determined using the new and the conventional remission criteria.

Patients and methods

Patients

The subjects included in this study were 122 patients diagnosed with RA under the 1987 ACR criteria [8] who were treated with TCZ from June 2008 to September 2009 according to data held by the TBCR [9, 10], and whose clinical progress could be followed for a period of 12 months or longer. The study was approved by the Ethics Committee of Tokyo KoseiNenkin Hospital, the Faculty of Medicine, Nagoya University (approval number: 1164) and other associated hospitals, and personal information about the patients was strictly protected.

TCZ therapy

The dose of tocilizumab administered for RA in Japan and Europe is 8 mg/kg, but the dose used in the United States is only 4 mg/kg. In this study, 8 mg/kg TCZ was administered every 4 weeks in accordance with the TCZ treatment guidelines of the Japan College of Rheumatology [11]. This dose, 8 mg/kg, was maintained from initiation to the end point. The methotrexate (MTX) dose administered was left to the judgment of the attending physician.

Therapeutic response

The response to TCZ was evaluated at 6 and 12 months after initiating treatment. The evaluation looked at changes in disease activity, using DAS28-ESR; remission was defined as DAS28-ESR <2.6 based on the revised EULAR criteria [12, 13]. Among the new criteria used to define remission (SDAI, CDAI, and the Boolean definition), we selected the Boolean criterion all ≤1 [tender joint count (TJC) ≤1, swollen joint count (SJC) ≤1, patient global assessment (PtGA) ≤1 cm, and C-reactive protein (CRP) ≤1 mg/dL] to denote remission [4].

Validation of recommendations and treat-to-target

To evaluate clinical response, we divided the 122 patients into 50 who had received TCZ as a first-line biological drug and 72 who were treated initially with an anti-TNF agent but had received TCZ as a second- or third-line biologic treatment. Then, under the presumption that treatment with TCZ starts early according to the concept of T2T, we further divided the 50 who had received TCZ as first-line treatment into a group of those with a disease duration at baseline of 12 months or less (≤12 M) and a group of those with a disease duration at baseline of more than 12 months (>12 M) (Fig. 1).

Validation of the new remission criterion

The percentages of the 122 patients who achieved remission under the new remission criterion (Boolean definition: all ≤1) and under the conventional remission criterion (DAS28-ESR <2.6) were calculated, and the baseline factors contributing to remission were identified for both situations. In order to examine differences in the remission rates seen with the new and the conventional criteria, we also analyzed the baseline characteristics in patients who had achieved remission under the conventional criterion but not under the new criterion, and those who had achieved remission according to both sets of criteria.

Statistical analysis

Efficacy in patients who discontinued administration was investigated on a last-observation-carried-forward basis. Fisher's exact test, Pearson's chi-square test, and the Wilcoxon rank sum test were used for comparisons between the two groups. The Wilcoxon signed-rank test was used to check for changes at 12 months after the initiation of TCZ treatment compared with baseline values

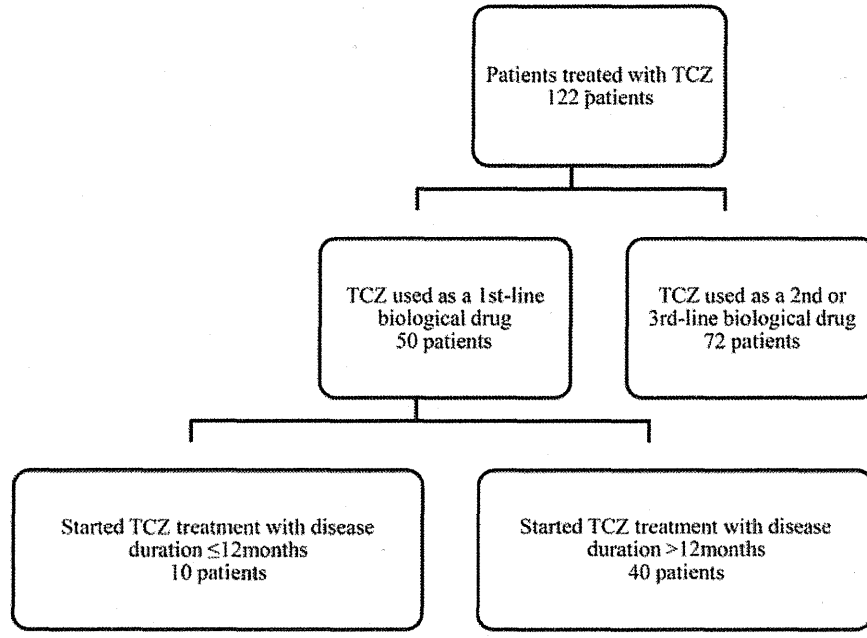

Fig. 1 Breakdown of the patients. *TCZ* tocilizumab

observed prior to treatment with TCZ. Significance was assessed based on a p value of 0.05. In order to identify the contributory factors when using the conventional remission criterion and the new remission criterion, a multivariate logistic regression model was employed to calculate the odds ratios adjusted for multiple variables and 95 % confidence limits. All statistical analyses were performed with the JMP version 9.0.2 statistical software package (SAS Institute Inc., Cary, NC, USA).

Results

The baseline characteristics of the 122 patients enrolled in this study are set out in Table 1. Their average age was 55.8 ± 13.5 years, mean disease duration was 124.1 ± 112.8 months, and 59.0 % (72/122) of them had been using an anti-TNF agent. Their average DAS28-ESR score prior to treatment with TCZ was 5.8 ± 1.3. In terms of previous anti-TNF agent use, 72 patients had and 50 patients had not previously received an anti-TNF agent, and corticosteroid usage was 80.6 % in the former set and 54.0 % in the latter ($p = 0.0017$). Baseline CRP prior to TCZ treatment was significantly higher in those who had previously used an anti-TNF agent, at 4.2 ± 3.1 mg/dL, than in those who had not, at 2.6 ± 2.2 mg/dL ($p = 0.0033$). Furthermore, on dividing the 50 patients who had received TCZ as a first-line biological drug into two groups (those with a disease duration at baseline of 12 months or less and those with a disease duration of longer than 12 months), the only apparent significant difference between the two groups was provided by their Steinbrocker stage scores [14] ($p = 0.0359$).

Therapeutic response to tocilizumab

The DAS28-ESR scores for the 122 patients were improved at 6 months ($p < 0.0001$), and the improvement was maintained at 12 months, going from 5.8 ± 1.3 at baseline to 3.2 ± 1.5 at 6 months and 3.0 ± 1.6 at 12 months (Fig. 2a). The remission rates according to the conventional criterion (DAS28-ESR <2.6) were 38.5 % at 6 months and 43.4 % at 12 months, and remission rates under the new criterion (Boolean definition: all ≤1) were 10.7 % at 6 months and 15.6 % at 12 months (Fig. 2b).

The evolution of DAS28-ESR over time did not change depending on whether anti-TNF agents had previously been used. The scores improved from 6.0 ± 1.4 at baseline to 3.3 ± 1.6 at 6 months and 3.0 ± 1.7 at 12 months in those who had previously used an anti-TNF agent, and from 5.6 ± 1.1 at baseline to 2.9 ± 1.5 at 6 months and 2.8 ± 1.5 at 12 months in those who had not (Fig. 2c). A trend for the remission rate of those who had previously used an anti-TNF agent to be higher than the remission rate of those who had not previously used an anti-TNF agent (48.0 % at 6 months and 50.0 % at 12 months versus 31.9 % at 6 months and 38.9 % at 12 months, respectively) under the conventional criterion was observed, but this difference in rate was not significant (Fig. 2d). Under the new criterion, there was a trend for remission to be higher in those who had not previously used anti-TNF agents

Table 1 Baseline characteristics of the rheumatoid arthritis patients treated with tocilizumab (TCZ) who were enrolled in the present study

	All cases (n = 122)						Prior use of anti-TNF agent		No prior use of anti-TNF agent (TCZ as 1st-line biologic)	
							With anti-TNF agent (n = 72)	Without anti-TNF agent (n = 50)	Baseline disease duration ≤12 months (n = 10)	Baseline disease duration >12 months (n = 40)
	Mean ± SD	Median	25th percentile	75th percentile	Min	Max	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Gender, female (%)	77.1						75.0	80.0	70.0	82.5
Age (years)	55.8 ± 13.5	59.0	46.0	66.0	24.0	82.0	55.0 ± 13.9	57.0 ± 13.0	56.8 ± 14.2	57.1 ± 12.9
RA duration (months)	124.1 ± 112.8	96.5	39.5	170.3	0	607.0	126.4 ± 117.0	120.9 ± 107.5	6.4 ± 4.5	149.6 ± 101.5
Steinbrocker stage scores (I/II/III/IV)	19/29/24/50						9/14/19/30	10/15/5/20	4/5/0/1	6/10/5/19
Steinbrocker class scores (1/2/3/4)	17/60/45/0						6/36/30/0	11/24/15/0	4/5/1/0	7/19/14/0
Previous anti-TNF agent use (%)	59.0						100.0	0.0	–	–
MTX use (%)	38.5						44.4	30.0	0.0	37.5
Baseline MTX dose (mg/week)	7.5 ± 2.0	8.0	6.0	8.0	2.0	12.0	7.6 ± 2.1	7.3 ± 2.0	–	7.3 ± 2.0
Corticosteroid use (%)	69.7						80.6	54.0	60.0	52.5
Prednisolone dose (mg/day)	4.7 ± 2.0	5.0	3.0	5.0	1.0	10.0	4.9 ± 2.0	4.3 ± 1.9	5.4 ± 2.5	3.9 ± 1.6
TJC (/28)	8.9 ± 7.4	6.5	4.0	12.0	0	28.0	9.6 ± 8.0	7.8 ± 6.3	8.4 ± 5.3	7.6 ± 6.6
SJC (/28)	7.1 ± 5.8	5.5	3.0	10.0	0	26.0	7.8 ± 6.6	6.1 ± 4.4	6.6 ± 3.7	5.9 ± 4.6
PtGA (mm)	55.6 ± 25.7	50.5	33.0	75.8	9.0	100.0	58.2 ± 26.7	51.9 ± 23.8	51.7 ± 27.8	52.0 ± 23.1
ESR (mm/h)	67.0 ± 34.3	65.5	40.0	94.3	2.0	100.0	70.6 ± 35.1	61.8 ± 32.7	71.4 ± 37.0	59.4 ± 31.7
CRP (mg/dL)	3.5 ± 2.9	3.1	1.2	5.1	0.1	17.7	4.2 ± 3.1	2.6 ± 2.2	2.6 ± 3.0	2.6 ± 2.0
DAS28-ESR	5.8 ± 1.3	5.7	4.9	6.6	2.1	9.2	6.0 ± 1.4	5.6 ± 1.1	5.8 ± 1.3	5.5 ± 1.0

SD standard deviation, *RA* rheumatoid arthritis, *TNF* tumor necrosis factor, *MTX* methotrexate, *TJC* tender joint count (28-joint count), *SJC* swollen joint count (28-joint count), *PtGA* patient global assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* 28-joint count disease activity score

(16.0 % at 6 months and 20.0 % at 12 months) than in those who had (6.9 % at 6 months and 12.5 % at 12 months), as was observed under the conventional criterion, but again this was not significant (Fig. 2d).

Then, presuming the application of the most recent EULAR recommendations and T2T, we divided the 50 patients who had received TCZ as a first-line biological drug into two groups [those with a disease duration at baseline of 12 months or less (≤12 M) and those with a disease duration at baseline of longer than 12 months (>12 M)]. In this situation, the DAS28-ESR scores were improved in both groups, changing from 5.8 ± 1.3 at baseline to 2.8 ± 1.6 at 6 months and 2.6 ± 1.4 at 12 months in the ≤12 M group, and from 5.5 ± 1.0 at baseline to 2.9 ± 1.4 at 6 months and 2.8 ± 1.6 at 12 months in the >12 M group. Thus, there was no significant difference between the changes seen in the two groups (Fig. 2e). Under the conventional criterion, the remission rates were comparable between the two groups: 50.0 % at 6 months and 50.0 % at 12 months in the ≤12 M group, and 47.5 % at 6 months and 50.0 % at 12 months in the >12 M group. Upon applying the new criterion, however, a difference appeared at 6 months, with remission rates of 40.0 % in the ≤12 M group against 10.0 % in the >12 M group (p = 0.0407). This disparity was maintained at the 12-month point as well, with remission rates of 50.0 % in the ≤12 M group against 12.5 % at 12 months in the >12 M group (p = 0.0181) (Fig. 2f).

Among the individual components of the new criterion (TJC ≤1, SJC ≤1, PtGA ≤1 cm, and CRP ≤1 mg/dL), the rate of achievement of PtGA ≤1 cm was significantly higher after 6 months in patients with a disease duration at baseline of 12 months or less (p = 0.0181) (Fig. 3).

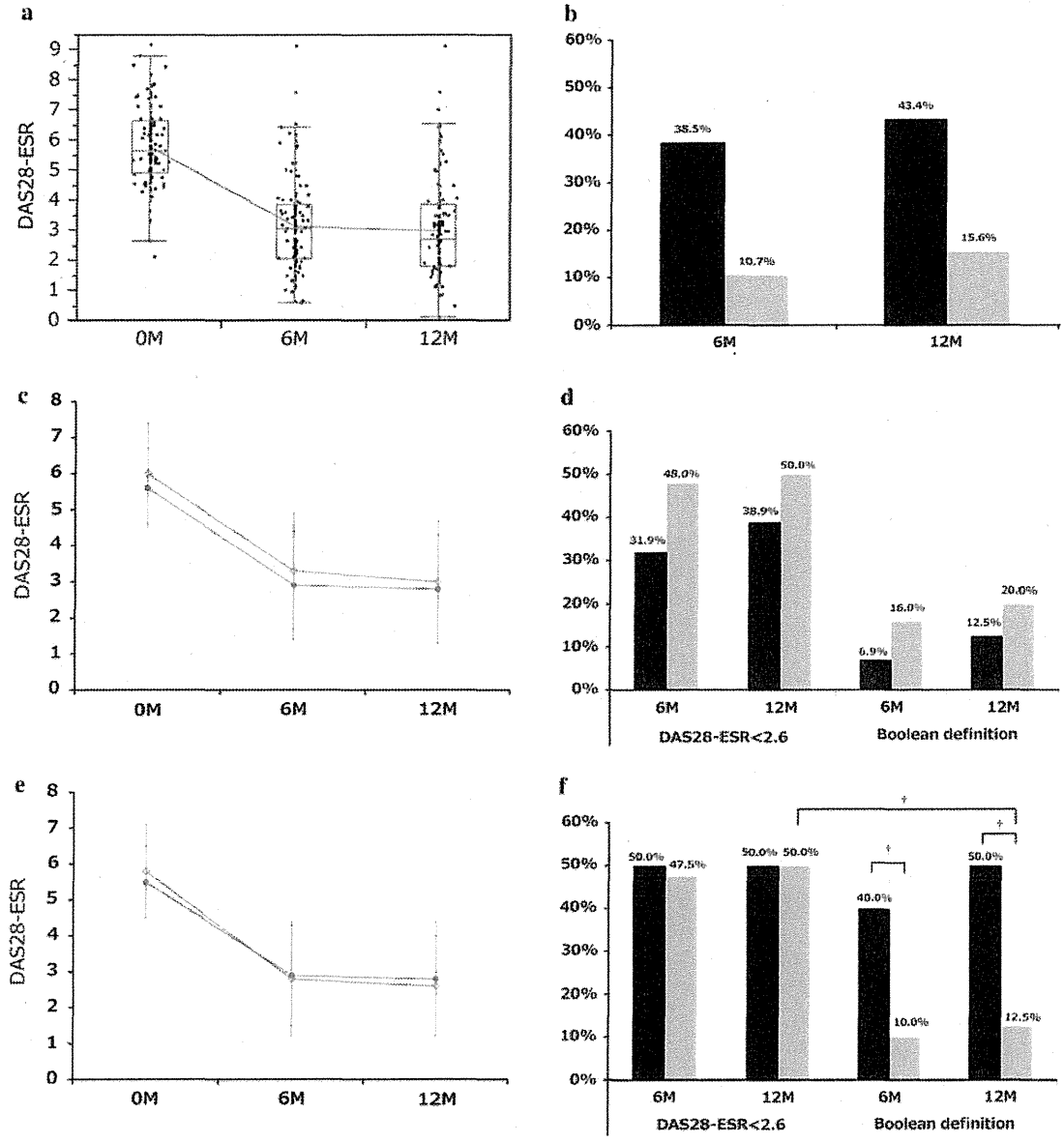

Fig. 2 Changes over time in DAS28-ESR, remission rates under the conventional criterion (DAS28-ESR <2.6), and remission rates under the new criterion (Boolean definition: all ≤1) in all patients ($n = 122$), in patients who had previously used anti-TNF agents, and by duration of disease at baseline (>12 vs. ≤12 months) for patients using TCZ as a first-line biologic. *DAS28* 28-joint count disease activity score, *ESR* erythrocyte sedimentation rate, *TNF* tumor necrosis factor, *6 M* 6 months, *12 M* 12 months. **a** Changes over time in DAS28-ESR in all patients ($n = 122$). The DAS28-ESR scores for the 122 patients were improved at 6 months ($p < 0.0001$). **b** Remission rates under conventional remission criteria (*black bars*) and new criteria (*gray bars*) in all patients ($n = 122$). **c** Changes over time in DAS28-ESR in patients who had previously used an anti-TNF agent (*empty squares*, $n = 72$) versus patients who had not previously used an anti-TNF agent (*filled circles*, $n = 50$). **d** Remission rates under the conventional and new criteria in patients who had (*black bars*) and had not (*gray bars*) previously used an anti-TNF agent. **e** Changes over time in DAS28-ESR by duration of disease at baseline in patients who used TCZ as a first-line biologic: disease duration ≤12 months (*empty squares*, $n = 10$) versus >12 months (*filled circles*, $n = 40$). **f** Remission rates under the conventional and new criteria by duration of disease at baseline in patients who used TCZ as a first-line biologic: disease duration ≤12 months (*black bars*) versus >12 months (*gray bars*). †Fisher's exact test, remission rate under the new criterion, >12 versus ≤12 months; 6 M ($p = 0.0407$), 12 M ($p = 0.0181$). Conventional criterion versus new criterion 12 M ($p < 0.0001$)

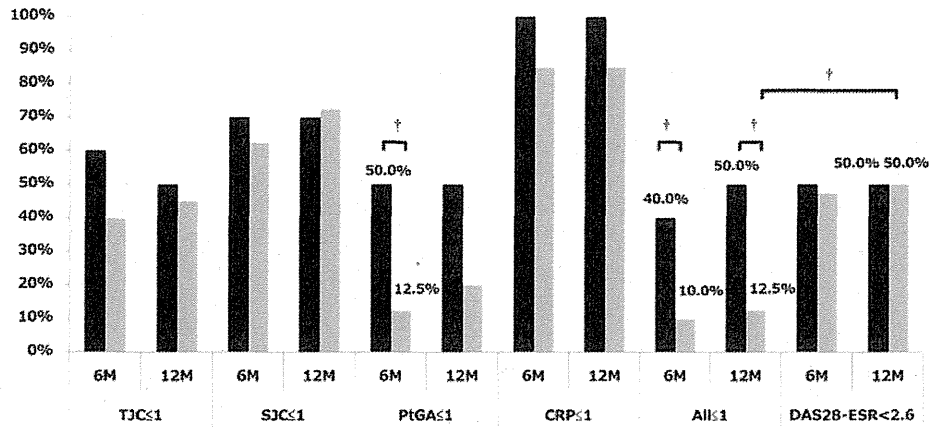

Fig. 3 Rates of achievement of TJC ≤1, SJC ≤1, PtGA ≤1 (cm), and CRP ≤1 (mg/dL) under the new remission criterion by duration of disease at baseline (>12 vs. ≤12 months) in patients using TCZ as a first-line biologic: *black bars* ≤12 months; *gray bars* >12 months. *TJC* tender joint count (28-joint count), *SJC* swollen joint count (28-joint count), *PtGA* patient global assessment, *CRP* C-reactive protein, *DAS28* 28-joint count disease activity score, *6 M* 6 months, *12 M* 12 months. †Fisher's exact test, >12 versus ≤12 months. PtGA ≤1: 6 M ($p = 0.0181$). All ≤1: 6 M ($p = 0.0407$), 12 M ($p = 0.0181$)

Table 2 Patient baseline factors for achieving remission at 12 months after the initiation of TCZ treatment under the conventional criterion and under the new criterion, and patient baseline factors in group A (those who did not meet the new criterion but met the conventional criterion) and group B (those who met both the new and conventional criteria), as determined by univariate logistic analysis

Baseline clinical parameters	Conventional remission		New remission		Group A/group B	
	Chi-square	*p* value	Chi-square	*p* value	Chi-square	*p* value
Gender	4.27	0.0387	0.05	0.8305	1.61	0.2048
Age	0.19	0.6619	3.32	0.0686	4.59	0.0321
RA duration	1.62	0.2038	9.65	0.0019	6.56	0.0105
Steinbrocker stage scores	3.54	0.0601	11.33	0.0008	8.38	0.0038
Steinbrocker class scores	4.73	0.0296	6.84	0.0089	3.40	0.0652
Previous anti-TNF agent use	1.48	0.2245	1.24	0.2649	0.35	0.5522
MTX use	1.80	0.1802	0.12	0.7273	0.12	0.7284
Corticosteroid use	7.30	0.0069	7.37	0.0066	2.48	0.1153
TJC	11.10	0.0009	2.15	0.1429	0.26	0.6131
SJC	6.89	0.0087	3.16	0.0753	0.56	0.4555
PtGA	11.14	0.0008	3.12	0.0773	0.02	0.9004
ESR	4.64	0.0312	2.68	0.1018	0.54	0.4633
CRP	0.30	0.5846	0.36	0.5500	0.77	0.3812
DAS28-ESR	14.59	0.0001	3.90	0.0482	0.00	0.9979

RA rheumatoid arthritis, *TNF* tumor necrosis factor, *MTX* methotrexate, *TJC* tender joint count (28-joint count), *SJC* swollen joint count (28-joint count), *PtGA* patient global assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* 28-joint count disease activity score, *Group A/group B* the patients were divided into group A, who met the conventional but not the new criterion (34 patients), and group B, who met both the conventional and new criteria (19 patients)

Identification of the factors that contribute to remission under the conventional and new criteria

Baseline data on gender, age, RA duration, stage, class, previous use of an anti-TNF agent, MTX use, corticosteroid use, TJC, SJC, PtGA, ESR, CRP, and DAS28-ESR for the patients treated with TCZ were used in a univariate logistic analysis (Table 2). The factors that multivariate logistic analysis identified as contributing to the achievement of remission at 12 months after the initiation of TCZ treatment under the conventional criterion were RA duration [odds ratio (OR) 0.9956, 95 % confidence interval (CI)

0.9910–0.9997], corticosteroid use (OR 0.2536, CI 0.0863–0.6876), TJC (OR 0.8698, CI 0.7866–0.9457), ESR (OR 0.9577, CI 0.9356–0.9772), and CRP (OR 1.7700, CI 1.3530–2.4636). The contributory factors under the new remission criterion were RA duration (OR 0.9787, CI 0.9644–0.9899), corticosteroid use (OR 0.2422, CI 0.0661–0.8210), SJC (OR 0.8109, CI 0.6723–0.9488), ESR (OR 0.9749, CI 0.9483–0.9989), and CRP (OR 1.4336, CI 1.0608–1.9684). The baseline items that contributed to remission according to both the conventional and new criteria were thus RA duration, corticosteroid use, and CRP. After assigning patients who had achieved remission under the conventional criterion but failed to do so under the new criterion to group A ($n = 34$), and those who had achieved remission under both the conventional and new criteria to group B ($n = 19$), we carried out multivariate analysis (note that no patient failed under the conventional criterion and succeeded under the new criterion only, and 69 patients failed to achieve remission under either the new or conventional criterion).

The analysis identified RA duration only (OR 1.0190, CI 1.0077–1.0343) (Table 3).

Discussion

In evaluations of the clinical response to TCZ using the conventional remission criterion of DAS28-ESR <2.6, the weights of CRP and ESR are higher than those of the TJC and SJC data [12, 13], which has been reported to give rise to disparately higher remission rates [15–18] than those indicated by the SDAI with the new remission criteria [4, 19], the CDAI [4, 20], or the Boolean definition [4].

However, those papers review the results for TCZ used in patients with a disease duration of about 10 years, and are not related to findings from investigations based on treatment guidelines or goals and remission criteria that seek to improve patient outcomes, such as those that have been proposed internationally in recent years.

In this study, we reviewed the progress of patients in the TBC registry who were started on TCZ treatment in the "early phase" of the disease; that is, those with an RA duration of 12 months or less at the initiation of TCZ treatment. Co-author Dr. Kojima previously reported that RA patients with a disease duration of <4.8 years that were treated with TCZ for 52 weeks showed a significantly higher remission rate than patients with a longer disease duration, based on DATA from TBCR [10]. However, in that work, we did not analyze early-phase RA patients who were treated with TCZ based on the recommendations of EULRA. In the present work, we found that if TCZ was given early and, moreover, as the first-line biological drug (in accordance with the EULAR recommendations), remission rates as high as 50.0 % at 12 months could be achieved using the new stricter remission criteria of the Boolean definition. We were also able to confirm that these findings were comparable with remission rates obtained based on the conventional criterion DAS28-ESR <2.6.

On the other hand, in patients with an RA duration exceeding 12 months, there was considerable disparity between the remission rates of 50 % obtained under the conventional criterion and 12.5 % under the new criterion

Table 3 Multivariate logistic analysis-based extraction of patient baseline factors for achieving remission under the conventional and new criteria, and extraction of patient baseline factors in group A (those who did not meet the new criterion but did meet the conventional criterion) and group B (those who met both the new and conventional criteria)

Baseline clinical parameters	Conventional remission		New remission		Group A/group B	
	Odds ratio (95 % confidence interval)	*p* value	Odds ratio (95 % confidence interval)	*p* value	Odds ratio (95 % confidence interval)	*p* value
Gender	–	–	4.4029 (0.9264–27.9475)	0.0836	0.2680 (0.0462–1.2500)	0.1113
Age	1.0348 (0.9963–1.0772)	0.0828	–	–	–	–
RA duration	0.9956 (0.9910–0.9997)	0.0413	0.9787 (0.9644–0.9899)	0.0012	1.0190 (1.0077–1.0343)	0.0040
Corticosteroid use	0.2536 (0.0863–0.6876)	0.0089	0.2422 (0.0661–0.8210)	0.0252	–	–
TJC	0.8698 (0.7866–0.9457)	0.0026	–	–	–	–
SJC	–	–	0.8109 (0.6723–0.9488)	0.0159	1.1935 (0.9316–1.6209)	0.1959
PtGA	0.9804 (0.9598–1.0001)	0.0567	–	–	–	–
ESR	0.9577 (0.9356–0.9772)	<0.0001	0.9749 (0.9483–0.9989)	0.0510	1.0249 (0.9945–1.0609)	0.1249
CRP	1.7700 (1.3530–2.4636)	0.0002	1.4336 (1.0608–1.9684)	0.0191	0.4951 (0.1380–1.4795)	0.2348

Multivariate logistic regression models (stepwise selection)

RA rheumatoid arthritis, *TNF* tumor necrosis factor, *MTX* methotrexate, *TJC* tender joint count (28-joint count), *SJC* swollen joint count (28-joint count), *PtGA* patient global assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* 28-joint count disease activity score, *Group A/group B* the patients were divided into group A, who met the conventional but not the new criterion (34 patients), and group B, who met both the conventional and new criteria (19 patients)

(Fig. 2f). If we consider the baseline characteristics (Table 1), this disparity appears to have been caused by differences in disease stage, which indicates the degree of disease progression.

The Health Assessment Questionnaire (HAQ) devised by Smolen and colleagues is constructed from an activity-related HAQ (ACT-HAQ) component and a damage-related HAQ (DAM-HAQ) component. It has been pointed out that the DAM-HAQ is correlated with the total Sharp score (TSS), and that if DAM-HAQ continues to worsen, no improvement in HAQ score can occur [21]. The salient points here are the effects arising from the irreversible progression of the disease and the poor correlation between clinical remission, such as that indicated by DAS representing inflammatory symptoms, and structural or functional remission.

Our study likewise indicated that, although an improved TJC or SJC (reflecting an improvement in inflammatory symptoms) may be seen, regardless of the disease duration (Fig. 3), only a small proportion of those with an RA duration exceeding 12 months at the initiation of TCZ treatment achieved PtGA $\leq$1 cm, and this had a major impact on the remission rate. Moreover, disease duration up to the initiation of TCZ treatment was also demonstrated to be a significant factor in achieving remission, not only under the conventional criterion but also under the new criterion (Table 3). In short, it appeared that patients with longer RA durations suffered irreversible progression of the disease, and that the PtGA could not be improved.

In summary, tocilizumab used as a first-line biological drug in patients with early-stage rheumatoid arthritis in accordance with the EULAR recommendations appears to provide high rates of remission, even under the new stricter criterion, and it can help to achieve the current goals of treatment.

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Conflict of interest N. Ishiguro received lecture fees (less than $10,000) from Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Chugai Pharma Corporation, Bristol-Myers Squibb, and Abbott Laboratories. T. Kojima and A. Kaneko also received lecture fees (less than $5,000) from these companies. The other authors declare no conflict of interest.

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ORIGINAL ARTICLE

Functional disability can deteriorate despite suppression of disease activity in patients with rheumatoid arthritis: a large observational cohort study

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Abstract
Objective To analyze the relationship between the progression of disability and disease activity in patients with rheumatoid arthritis (RA) in daily practice.
Methods Patients from an observational cohort, IORRA, who completed surveys during 2009–2011 were eligible. Linear regression of disease activity score 28 (DAS28), Japanese version of Health Assessment Questionnaire (J-HAQ), and EQ-5D from baseline were calculated, and the angles of the regression lines were designated DAS28 slope, J-HAQ slope, and EQ-5D slope, respectively, in each patient; averages were compared between treatment groups.
Results A total of 5,038 patients [84.0 % female, mean age 59.4 (SD 13.1) years, disease duration 13.2 (9.6) years, DAS28 3.29 (1.14), and J-HAQ 0.715 (0.760)] were analyzed. The average DAS28 slope indicated improvement in all groups, whereas J-HAQ slopes were negative in patients on methotrexate (MTX), biologics, combination biologics/disease-modifying antirheumatic drugs (DMARDs), and combination biologics/MTX at baseline, but positive in patients on prednisolone >5 mg/day [0.010 (0.153)] and not on MTX at baseline [0.007 (0.122)], representing a worsening of disability.
Conclusion There is some disparity between improvement of disease activity and progression of disability, suggesting that quality of remission must be considered.

Keywords Rheumatoid arthritis · Disease activity · Physical function · Treatment · Cohort study

Introduction

Treatment of rheumatoid arthritis (RA) has improved over the last ten years, following the introduction of new agents and modification of treatment strategies [1, 2]. As a consequence, clinical remission has become a realistic goal [3, 4]. Suppression of disease activity is the major factor that inhibits the progression of disability [1, 5, 6]. Since the treat-to-target (T2T) initiative first proposed the strategy of remission induction in the management of RA in daily practice [7, 8], the proportion of patients in remission has been increasing. In the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort, which we established at the Institute of Rheumatology, Tokyo Women's Medical University in 2000, the improvement in the disease activity in RA patients has been quite apparent, and nearly 40 % of all patients in 2011 achieved clinical remission [9]. This is thought to be the result of improved patient care following the recognition of the importance of remission induction in preventing joint destruction and preserving activities of daily living. However, disability in patients in the IORRA cohort has not improved as much as disease activity: the average disease activity score 28 (DAS28) improved from 4.16 in 2000 to 3.03 in 2011 (−28 %), while the Japanese version of Health Assessment Questionnaire (J-HAQ) score only improved from 0.80 in 2000 to 0.64 in 2011 (−18 %). This triggers the question of whether the

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remissions achieved by biologics versus corticosteroids yield comparable outcomes with respect to disability.

We hypothesized that the discrepancy between improvement in disease activity and progression of disability might depend on which agents are administered. Indeed, we have previously demonstrated that patients treated with corticosteroids develop progressive disability even when they are in remission, and suggested that there is a difference in the quality of remission between different agent classes [10, 11]. In the study described in this report, we analyzed the relationship between control of disease activity and progression of disability in our observational cohort, IORRA.

Patients and methods

Patients and the IORRA database

We established a prospective observational cohort of RA patients at the Institute of Rheumatology, Tokyo Women's Medical University in October 2000; this is designated the IORRA cohort. Patients with RA who fulfilled the American College of Rheumatology criteria for RA [2, 12, 13] were registered, and their information and data were collected biannually (in April and October) when patients visited the outpatient unit of our institute for consultation. Informed consent was routinely obtained from each patient at each visit.

The IORRA database consists of three components. The first component is the physician's evaluation, which includes the number of tender joints, number of swollen joints, and a visual analogue scale (VAS) of disease activity rated by the physician. The second component is information collected from patients, which includes VAS for pain, VAS for general health, disability level using J-HAQ score [12], height, body weight, and comorbidities in the previous six months. Information about medication actually taken (not just prescribed) during the period was also reported, including corticosteroid use and daily dose, disease-modifying antirheumatic drug (DMARD) use, methotrexate (MTX) use and weekly dose, and biologics use. Patients were asked by the attending physician to answer these questions by completing questionnaire sheets at home and mailing them back in a pre-stamped envelope within two weeks of their visit. The third component is laboratory data, including C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), blood cell count, liver transaminase levels, and urinalysis. All information was integrated into a single database that was used for analysis. DAS28 and EQ-5D scores were calculated according to the original methods [14, 15].

Over 99 % of RA patients in our institute participated in the study during this time period, and over 98 % of patients completed and returned their questionnaires. Patients who participated in the IORRA survey between April 2009 and April 2011 were eligible for this study.

Methods

Institute of Rheumatology, Rheumatoid Arthritis is an observational cohort database in which longitudinal data about disease activity, disability, and treatment have been collected. The linear regressions of DAS28, J-HAQ, and EQ-5D scores from baseline were calculated for each patient, and the angles of the regression lines were designated the DAS28 slope, J-HAQ slope, and EQ-5D slope, respectively. Specifically, for each patient who participated in IORRA at least three times during the study period, a linear regression was conducted with longitudinal DAS28, J-HAQ, and EQ-5D as a response and continuous time, 0, 1, 2, and 3 as an explanatory variable. The DAS28 slope increases as disease activity worsens, the J-HAQ slope increases as disability progresses, and the EQ-5D slope increases as quality of life improves.

Average values for the DAS28 slope, J-HAQ slope, and EQ-5D slope were calculated for different patient groups as follows: (a) patients receiving MTX were classified by MTX dose, (b) patients on oral corticosteroids were classified by equivalent prednisolone (PSL) dose, and (c) patients were classified by agents used at baseline: on conventional DMARDs other than MTX, on MTX, on biologics, and on a combination of DMARDs and biologics or a combination of MTX and biologics. At baseline in April 2009, four biologics were available in Japan: infliximab, etanercept, adalimumab, and tocilizumab. The average DAS28 slope, J-HAQ slope, and EQ-5D slope were compared between treatment groups, respectively. Written consent was obtained from each patient who participated in the study, according to the Declaration of Helsinki (most recently revised at the General Assembly in October 2008), and the study was approved by the local ethics committee at Tokyo Women's Medical University.

Statistical analysis

Means and their standard deviations were used to describe data for continuous variables, and proportions were used to describe data for discrete variables. The time coefficients, representing the degree of progression for each outcome in each patient, were analyzed using the mean and its 95 % confidence interval according to the treatment the patient received. The distributions of the DAS28 slope, J-HAQ slope, and EQ-5D slope were visualized by plotting the

cumulative probability [16–18], a method that has been commonly used to present radiographic progression in RA clinical studies, in order to highlight differences in the DAS28 slope, J-HAQ slope, and EQ-5D slope between treatment groups. All of the calculations were done using the statistical software R (http://cran.r-project.org/, version 2.14.0).

Results

Baseline characteristics

A total of 5,038 patients [84.0 % female, mean age 59.4 (SD 13.1) years, disease duration 13.2 (9.6) years at baseline] whose data from consecutive visits were available were recruited from the cohort.

The average DAS28, J-HAQ, and EQ-5D scores at baseline were 3.29 (1.14), 0.715 (0.760), and 0.760 (0.174), respectively. Patients were subclassified by treatment at baseline (April 2009). The baseline characteristics of these treatment groups are shown in Table 1 and in Tables S1, S2, S3, and S4 of the Electronic supplementary material (ESM).

Table 1 Baseline demographic and disease characteristics

Characteristics	Study population (N = 5,038)
Age (years)	59.4 (13.1)
Women (%)	84.0
Duration (years)	13.2 (9.6)
DAS28	3.29 (1.14)
CDAI	7.56 (6.48)
SDAI	8.28 (7.04)
EQ-5D	0.76 (0.17)
J-HAQ (0–3 scale)	0.715 (0.760)
Tender joint count (0–45)	1.8 (3.2)
Swollen joint count (0–45)	1.9 (2.8)
Pain VAS (0–100 scale)	28.7 (25.2)
Patient global VAS (0–100 scale)	30.3 (24.6)
Physician global VAS (0–100 scale)	15.6 (15.2)
CRP (mg/dl)	0.73 (1.27)
ESR (mm/h)	31.7 (22.9)
DMARDs (%)	91.0
MTX (%)	68.5
MTX dose (mg/week)	8.0 (3.1)
Prednisolone (%)	46.8
Prednisolone dose (mg/day)	4.2 (2.9)
Biologics (%)	8.7

Values are the mean (SD) unless indicated otherwise

DAS28 disease activity score 28, *CDAI* clinical disease activity index, *SDAI* simplified disease activity index, *J-HAQ* Japanese version of Health Assessment Questionnaire, *VAS* visual analogue scale, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DMARDs* disease-modifying anti-rheumatic drugs, *MTX* methotrexate

DAS28 slope

The DAS28 slopes of each treatment group are shown in Table 2. During the observation period, the average DAS28 slope was negative (i.e., it sloped downward) in all subgroups, indicating improvement in disease activity in all subgroups.

J-HAQ slope

The J-HAQ slopes in each treatment group are shown in Table 3. The J-HAQ slope was negative in patients who were receiving MTX, biologics, a combination of biologics and DMARDs, and a combination of biologics and MTX at baseline. In contrast, the J-HAQ slope was positive (i.e., it sloped upward) in patients receiving >5 mg/day of PSL [0.010 (0.153)] and in those without MTX [0.007 (0.122)] at baseline, indicated worsening functional disability.

EQ-5D slope

The EQ-5D slopes in each treatment group are shown in Table 4. The EQ-5D slope was positive in all treatment groups. A significant dose response of EQ-5D was observed in the MTX groups, and the largest improvement in EQ-5D was observed in patients who were on biologics + DMARDs/MTX at baseline. In addition, the increase in EQ-5D slope was larger in the MTX groups than in the PSL groups.

Distribution of the J-HAQ slope

The distribution of the J-HAQ slope was visualized using the probability plot method (Fig. 1). Each plot successfully shows the difference in the J-HAQ slope among groups.

Discussion

In this study, we developed the concept of DAS28 slope, J-HAQ slope, and EQ-5D slope to assess changes over a specified time period. In clinical studies, delta DAS28 and delta HAQ are often used to indicate changes between two time points, i.e., the baseline and endpoint. However, in our longitudinal observational study, DAS28, J-HAQ, and EQ-5D scores were recorded at multiple time points, and these values fluctuated over time; thus, we considered it more logical to evaluate the changes by analyzing linear regression using multiple values at multiple time points. Thus, the DAS28 slope, J-HAQ slope, and EQ-5D slope are

Table 2 DAS28 at baseline and DAS28 slopes

	N	DAS28 (95 % CI)	DAS28 slope (95 % CI)
All	5,038	3.29 (3.26 to 3.33)	−0.071 (−0.080 to −0.061)
Not on MTX	1,586	3.22 (3.16 to 3.28)	−0.041 (−0.058 to −0.025)
MTX 0–4 mg/week	488	3.30 (3.20 to 3.40)	−0.068 (−0.100 to −0.037)
MTX 4–6 mg/week	827	3.28 (3.20 to 3.36)	−0.069 (−0.091 to −0.047)
MTX 6–8 mg/week	966	3.34 (3.26 to 3.41)	−0.083 (−0.104 to −0.062)
MTX 8–10 mg/week	627	3.38 (3.30 to 3.47)	−0.093 (−0.118 to −0.068)
MTX >10 mg/week	521	3.35 (3.26 to 3.44)	−0.106 (−0.131 to −0.081)
Not on PSL	2,682	3.10 (3.06 to 3.15)	−0.056 (−0.068 to −0.044)
PSL 0–3 mg/day	996	3.36 (3.29 to 3.43)	−0.075 (−0.095 to −0.055)
PSL 3–5 mg/day	873	3.56 (3.49 to 3.63)	−0.087 (−0.110 to −0.064)
PSL >5 mg/day	487	3.73 (3.62 to 3.83)	−0.112 (−0.144 to −0.080)
DMARDs	4,587	3.29 (3.26 to 3.33)	−0.071 (−0.080 to −0.061)
MTX	3,429	3.33 (3.29 to 3.37)	−0.083 (−0.094 to −0.072)
Biologics	437	3.28 (3.17 to 3.39)	−0.104 (−0.135 to −0.073)
MTX monotherapy	1,944	3.28 (3.24 to 3.33)	−0.066 (−0.080 to −0.052)
Biologic monotherapy	74	3.28 (3.05 to 3.51)	−0.079 (−0.146 to −0.012)
Biologic with DMARD	363	3.28 (3.15 to 3.41)	−0.109 (−0.144 to −0.074)
Biologic with MTX	345	3.25 (3.12 to 3.38)	−0.107 (−0.143 to −0.071)

CI confidence interval

Table 3 J-HAQ at baseline and J-HAQ slopes

	N	J-HAQ (95 % CI)	J-HAQ slope (95 % CI)
All	5,038	0.715 (0.693 to 0.735)	−0.001 (−0.004 to 0.002)
Not on MTX	1,586	0.690 (0.651 to 0.729)	0.007 (0.000 to 0.013)
MTX 0–4 mg/week	488	0.772 (0.697 to 0.848)	0.001 (−0.010 to 0.011)
MTX 4–6 mg/week	827	0.727 (0.673 to 0.780)	−0.004 (−0.012 to 0.003)
MTX 6–8 mg/week	966	0.733 (0.686 to 0.780)	−0.003 (−0.010 to 0.003)
MTX 8–10 mg/week	627	0.680 (0.628 to 0.732)	−0.005 (−0.014 to 0.004)
MTX >10 mg/week	521	0.703 (0.646 to 0.759)	−0.013 (−0.021 to −0.004)
Not on PSL	2,682	0.542 (0.517 to 0.567)	−0.004 (−0.008 to 0.000)
PSL 0–3 mg/day	996	0.848 (0.797 to 0.897)	0.001 (−0.006 to 0.007)
PSL 3–5 mg/day	873	0.899 (0.847 to 0.952)	0.000 (−0.008 to 0.008)
PSL >5 mg/day	487	1.062 (0.987 to 1.138)	0.010 (−0.004 to 0.024)
DMARDs	4,587	0.705 (0.683 to 0.726)	−0.001 (−0.004 to 0.002)
MTX	3,429	0.723 (0.698 to 0.748)	−0.005 (−0.008 to −0.001)
Biologics	437	0.917 (0.843 to 0.990)	−0.016 (−0.026 to −0.006)
MTX monotherapy	1,944	0.694 (0.661 to 0.727)	−0.002 (−0.007 to 0.003)
Biologic monotherapy	74	1.193 (0.990 to 1.395)	−0.006 (−0.029 to 0.016)
Biologic with DMARD	363	0.861 (0.783 to 0.938)	−0.018 (−0.029 to −0.007)
Biologic with MTX	345	0.853 (0.773 to 0.934)	−0.022 (−0.033 to −0.010)

essentially analogous to delta DAS28, delta J-HAQ, and delta EQ-5D, respectively; however, we consider the former to be more logical indicators of changes over time in the IORRA observational cohort study.

The baseline characteristics of the treatment groups in this analysis differed, so it is not appropriate to compare the results between treatment groups. This is an inherent limitation of observational studies, in contrast to well-designed clinical trials [19]. It may be possible to compare outcomes by matching patients with comparable disease activity or disability, as done in propensity score matching [20], in order to determine which treatment is superior for

Table 4 EQ-5D at baseline and EQ-5D slopes

	N	EQ-5D (95 % CI)	EQ-5D slope (95 % CI)
All	5,038	0.76 (0.76 to 0.76)	0.0046 (0.0032 to 0.0059)
Not on MTX	1,586	0.77 (0.76 to 0.78)	−0.0008 (−0.0037 to 0.0022)
MTX 0–4 mg/week	488	0.76 (0.74 to 0.78)	0.0046 (0.0005 to 0.0086)
MTX 4–6 mg/week	827	0.76 (0.75 to 0.78)	0.0061 (0.0027 to 0.0095)
MTX 6–8 mg/week	966	0.75 (0.74 to 0.76)	0.0072 (0.0043 to 0.0100)
MTX 8–10 mg/week	627	0.76 (0.74 to 0.77)	0.0075 (0.0042 to 0.0108)
MTX >10 mg/week	521	0.75 (0.73 to 0.76)	0.0082 (0.0049 to 0.0115)
Not on PSL	2,682	0.80 (0.79 to 0.81)	0.0051 (0.0032 to 0.0069)
PSL 0–3 mg/day	996	0.74 (0.73 to 0.75)	0.0047 (0.0018 to 0.0076)
PSL 3–5 mg/day	873	0.72 (0.71 to 0.73)	0.0042 (0.0009 to 0.0074)
PSL >5 mg/day	487	0.67 (0.66 to 0.69)	0.0022 (−0.0034 to 0.0077)
DMARDs	4,587	0.76 (0.76 to 0.77)	0.0049 (0.0035 to 0.0063)
MTX	3,429	0.76 (0.75 to 0.76)	0.0068 (0.0053 to 0.0083)
Biologics	437	0.73 (0.71 to 0.74)	0.0120 (0.0074 to 0.0165)
MTX monotherapy	1,944	0.76 (0.75 to 0.77)	0.0053 (0.0033 to 0.0073)
Biologic monotherapy	74	0.69 (0.65 to 0.73)	0.0079 (−0.0045 to 0.0203)
Biologic with DMARD	363	0.73 (0.71 to 0.75)	0.0128 (0.0079 to 0.0177)
Biologic with MTX	345	0.73 (0.72 to 0.75)	0.0135 (0.0084 to 0.0186)

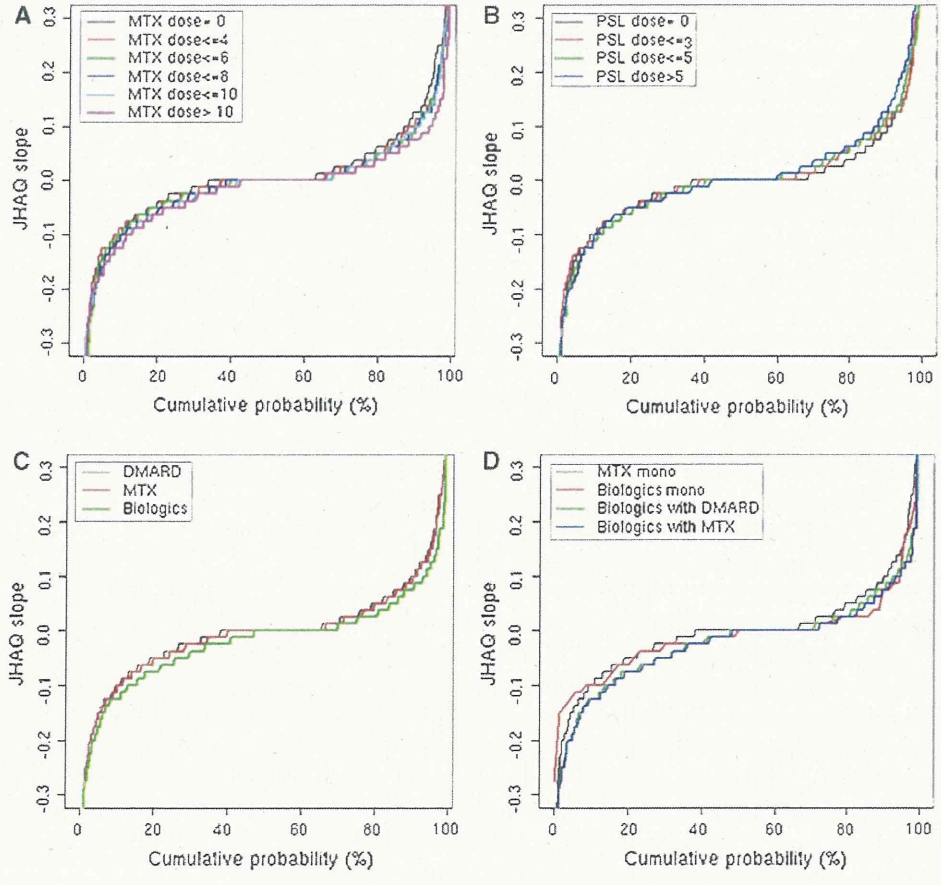

Fig. 1 Probability plots of J-HAQ slopes described for groups subclassified by **a** MTX dose, **b** PSL dose, **c** DMARD, MTX, or biologics users, and **d** monotherapy of MTX/ biologics and combination therapies

the prevention of disability. However, the goal of this study was to examine the differences between control of disease activity as estimated by DAS28 and progression of disability as estimated by J-HAQ among the different treatment groups.

As indicated by the DAS28 slope shown in Table 2, an improvement in DAS28 was observed in every treatment group during the two years from baseline, indicating that the treatment successfully improved the signs and symptoms of RA. Biologics strikingly decreased DAS28 with or without DMARDs, and PSL also decreased DAS28 in a dose-dependent manner. As indicated by the EQ-5D slope, patient QOL also improved during the observation period. However, the J-HAQ slopes differed markedly between treatment groups. Dramatic decreases in the J-HAQ slope were seen in patients on biologics, as well as in patients on MTX (in a dose-dependent manner), whereas increases were observed in patients on PSL dosed at >5 mg/day, indicating worsening functional disability.

These data were also visualized using probability plots. As this method has been frequently used to visualize the distribution of the progression of bone damage as assessed by X-ray scoring methods, we elected to utilize it to show progression of disability. Biologics, sufficiently dosed MTX, and low-dose PSL suppressed this ratio, indicating that patients in these groups are treated properly with respect to preventing the progression of disability. While similar results have been reported from clinical trials [21], the present data reflect patients seen in actual clinical practice.

As proposed in the T2T initiative, the primary target for treatment of RA should be clinical remission [1–4]. As mentioned above, we previously reported that patients treated with corticosteroids experience progression of disability even when they are in remission, and we suggested that there is a difference in the quality of remission between different agent classes [10, 11]. The present study supports this finding and suggests that there should be some discrepancy between suppression of disease activity and maintenance of physical function.

Another mechanism of joint damage prevention in well-controlled RA patients may be the consequence of residual disease activity [22, 23]. We have used DAS28 as a measure of disease activity; however, the progression of disability may be caused by the involvement of joints other than the 28 joints used in this assessment.

A major limitation of this study is the observational nature of the study design; thus, outcomes could not be accurately compared between treatment groups. Indeed, it is also true that the selection of the baseline treatment may be strongly associated with the baseline patients' comorbidities or previous drug histories, etc. Therefore, these background characteristics may influence the outcomes of groups categorized according to the type of agent selected. Our present data do not indicate that corticosteroid should never be given on any occasion in daily practice, or that corticosteroid itself worsens functional disability. In addition, treatment group assignment was based on the treatment at baseline, so the effects of changes in treatment during the observational period could not be assessed.

In conclusion, there is considerable disparity between control of disease activity and progression of disability in RA patients, and this disparity is correlated with the type and dosage of agent used. Remission is a realistic target under current management guidelines; however, differences in the quality of remission must also be considered.

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EBMの普及と医療リテラシー：情報と医師患者コミュニケーション

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Key words　根拠に基づく医療(Evidence-based medicine：EBM)，ヘルスリテラシー，ヘルス・コミュニケーション，診療ガイドライン，shared decision-making（共有決定）

1．根拠に基づく医療（EBM）の誕生と普及

1991年にカナダのGuyattが提唱した根拠に基づく医療(Evidence-based medicine：EBM)は，質の高い医療を求める社会的な意識の高まりと共に，臨床各分野で急速に普及した．EBMは「臨床家の勘や経験ではなく科学的根拠(エビデンス）を重視して行う医療」と言われる場合があるが，本来は，「臨床研究によるエビデンス，医療者の専門性・熟練と患者の価値観の3要素を統合し，よりよい患者ケアのための意思決定を行うもの」である．近年では，これに「環境－個々の臨床状況とセッティング」が追加され，医療の行われる「場」や固有の状況の重要性が強調されている．

「臨床研究によるエビデンス」とは，人間集団を対象とする疫学的手法（臨床試験を含む）で得られた一般論であり，「医療者の専門性・熟練(expertise)」とは，臨床の現場で貴重な個々の経験の積み重ねから得られる直観的な判断力と言える．本稿ではEBMの実践の本来の対象であり，目標と言える患者側の要因について，近年関心が高まっているヘルスリテラシー，そして患者と医療者の相互作用のプロセスであるコミュニケーションの課題について述べ，医療における新しい意思決定のあり方としてのshared decision-making（共有決定）の可能性を考えたい．

2．医療におけるリテラシーとコミュニケーション

リテラシーとは「読み書き能力．また，与えられた材料から必要な情報を引き出し，活用する能力．応用力」(大辞泉）である．ヘルスリテラシーはWHOのHealth Promotion Glossaryでは「認知や社会生活上のスキルを意味し，良好な健康の増進・維持に必要な情報にアクセスし，理解し，利用するための個人の意欲や能力」(1998)とされている．また米国医学研究所によると「健

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康に関する適切な意思決定をして，治療の指示に従うために必要となる，基本的な健康情報とサービスを，獲得，処理，理解できる能力」(2004)と定義される．「ヘルス(health)」という言葉は，国内では（臨床）医学（medicine）に対して，予防医学のように「健康」を扱う領域がイメージされがちだが，一般的に海外ではその両者を幅広く含む．本稿の題名の医療リテラシーは，ヘルスリテラシーの中で，特に狭義の医療の場が想定されたものと言える．以下，海外の通例にならって，広くヘルスリテラシーとして本論を進める．

ヘルスリテラシーには，健康上のリスクと医療サービスの利用に関する事実情報の伝達の基本となる機能的ヘルスリテラシーから，他者との協力的な環境を作り出す個人的な能力としての相互的ヘルスリテラシー，それが個人を越えて社会的・組織的に発展する批判的ヘルスリテラシーの３タイプがあるとされている(Nutbeam, Health Promotion International 2000)．まず基盤となる機能的ヘルスリテラシー，すなわち「健康・身体・医療・疾病を表す言葉が理解されていない」ことが注目され，1990年代に単語リストを正確に発音できたものを点数化するRapid Estimate of Adult Literacy in Medicine (REALM)や，穴埋め式で医療用語の読解力をみるFunctional Health Literacy in Adults (TOHFLA)などが開発された．ヘルスリテラシーが低いと医学知識が乏しく（喘息患者で吸入器の使い方が分からない，糖尿病患者は低血糖症状を知らない，高血圧患者で減量と運動が血圧を下げることを知らない，温度計の読み方を理解できない等），健康習慣が少ない(喫煙習慣が多い，定期的な検診を受けない等）ことが指摘されてきた．

米国IOMは，2001年の報告書“Crossing the Quality Chasm”において，「良質な医療とは，患者に対して，高い技術レベルで，意思疎通を十分にとり，患者参加の意思決定アプローチで，文化的相違を尊重しながら，適切なサービスを提供すること」と述べ，患者，さらには社会のヘルスリテラシーが医療の質を左右する可能性を示唆している．

このように近年では，患者のヘルスリテラシーを医療者が理解し，時にはその向上を支援し，時にはその実状に合わせて医療を提供する関係を構築することが，医療者に求められる新たに臨床的な課題となった．米国医師会は，医師が患者のヘルスリテラシーを理解することで医療の安全性を高める取り組みの中で，「…コミュニケーションは，効果的な医療提供において必須であり，臨床医がもつ最も力強い武器である．不幸にも，臨床医のコミュニケーションレベルと患者の理解レベルに，ずれがある．事実，患者はしばしば臨床医が与える情報の多くを誤解したり，理解しない．この理解不足は，服薬ミス，診療予約ミス，副作用，そして医療過誤訴訟まで発展することもある．」(Weiss BD, 2007)として，患者のリテラシーとコミュニケーションの両面で医療者の関心と注意を喚起している．このように欧米諸国では，薬剤，処置，手術に次ぐ第４の医療技術として，医療者と患者をつなぐコミュニケーションへの関心が急速に高まり，患者の生命予後，QOLの重要な規定因子であるという認識が一般化しつつある．コミュニケーションの広大な領域の中で，医療，そして「ヘルス(health)」をテーマとする分野はヘルス・コミュニケーションと呼ばれる．表に米国医師会の“Health literacy and patient safety：Help patients understand”からコミュニケーションを改善する提案を紹介する．

3. 不確実なリスク情報とどう向き合うか？

ヘルスリテラシーの基本となる機能的リテラ

表

患者との個人間のコミュニケーションを改善する６つのステップ

1. ゆっくり話す
   - ゆっくり話し，少しだけ患者一人あたりの時間を増やすことでコミュニケーションは改善する．そうすれば医師–患者関係をより患者中心のものにできる
2. 簡単で医学的ではない言葉を使う
   - 祖母に説明するように，患者に説明する
3. 絵を見せる，または描く
   - ビジュアルな画像は患者の考えを整理するのに役立つ
4. 提供する情報量を限定する，そして繰り返す
   - 情報は目前の課題についてだけ（少し）与えられると最も記憶される．繰り返すことで記憶が定着する
5. “teach-back”（復唱）法をつかう
   - 伝えたことを患者に復唱してもらい，患者の理解を確認する
6. 恥をかかせない環境をつくる：質問を促す．
   - 患者が質問しやすいようにする．下記の「3つの質問をして下さい」を考慮．患者の家族または友人にも協力を求める．

コミュニケーション改善の工夫

1. “teach-back”（復唱）法
   - 患者に「わかりましたか？」とは聞かない
   - 代わりに提案する治療または介入に，どれくらい取りかかるつもりか，患者に説明あるいは図示してもらう
   - もし患者が正確に説明しなかったら，こちらの指導が不十分だったと考える．別の方法で情報を再度提供する
2. “The Ask-Me-3 questions”（「3つの質問をして下さい」）
   - 「私の一番の問題は何ですか？」
   - 「私は何をすればよいですか？」（自分の問題について）
   - 「なぜ，これをすることが自分にとって重要なのですか？」

（Health literacy and patient safety：Help patients understandより）

シーでは，再診日の確認や服薬指導といった「（ほぼ）確実」な情報を，医療者が患者に伝え，それを患者が理解して実施できるかどうかが主題となる．このレベルの問題も，医療現場で日常的に頻発する大きな課題であることは間違いなく，さまざまなコミュニケーション戦略で，その状況の改善が試みられている．しかし，さらに問題となる状況は，医療者と患者が共有しようとする情報が不確実（uncertainty）な場合，さらには既存の関連情報がほとんど無いような状況でのリテラシー（相互的リテラシー～批判的リテラシー）とコミュニケーションである．

健康や医療に関する情報は不確実な部分が多い．「EBMは白黒をつけるもの」ではなく，疫学を基盤に多くの情報は灰色であること，灰色の情報がどれくらいの灰色か（白に近いか，黒に近いか）を見きわめる知識を体系化したとも言える．一方，意思決定は「する・しない」の二つに一つであり，灰色の情報から白黒の決定への飛躍が求められる．前述のとおり，根拠に基づく意思決定は決してevidenceだけで決まるのではなく，意思決定を行う個人の一政策であれば社会の一value（価値観），そして利用可能なresource（資源）が大きく影響する．

しかし人間集団を対象としたエビデンスが得られても，その伝え方には多くのバリエーションがあり，その示し方で患者（医療者も）の認知や意思決定が変わる可能性も指摘されている．米国の著名なメディカルライター・Lang Tは，前立腺がんの治療に関する臨床試験から得られる2×2表から9種類の異なるリスク指標（死亡数，絶対リスク，自然頻度，相対リスク，絶対

リスク減少，相対リスク減少，オッズ，オッズ比，治療必要数)が得られることを示している．このようなエビデンスをどのように蓄積し，どのように伝達し，医療者と患者が共有していくか，EBMの枠組みは患者と医療者のコミュニケーションの大きな課題を問いかけている．

4. エビデンスから診療ガイドラインへ

近年，既存のエビデンスのレビューに基づいた診療ガイドラインの整備が各領域で進められている．診療ガイドラインは米国医学研究所の定義によると「特定の臨床状況のもとで，臨床家と患者の意思決定を支援する目的で，系統的に作成された文書」(1990)であり，「エビデンスの系統的レビューに基づき，患者ケアの最適化を目的とする推奨を含む文書」(2011)とされる．国内では公益財団法人日本医療機能評価機構Mindsが，EBMの手法で作られた診療ガイドラインや関連情報を幅広く無料で提供している．

診療ガイドラインは法律的な拘束力はないが，“soft law”と捉える考え方がある．その原理は“Comply or explain principle”，すなわち「ふつうはその通りにせよ，しない場合は，その理由を説明せよ」という考え方である．診療ガイドラインで述べられている推奨が当てはまる患者にはまずそのように説明した上で行う．しかし，患者によっては何らかの理由で行わない方が良いと判断される場合もある（年齢，併存症の状態，アレルギー歴など)．その場合は理由を患者に（可能な場合には）説明して了解を得て，診療ガイドラインで他に推奨されている（それが無い場合は臨床家の知識と経験に照らして最良と考える)別の方法を行う，という対応である．

一般的には「診療ガイドラインが当てはまる患者は60–95%」とされている（Eddy JAMA 2001)が，“soft law”のように用いれば，臨床家が診療ガイドラインの推奨を実施する・しないにかかわらず，その判断の根拠として診療ガイドライン自体はいつでも用いることができ，診療ガイドラインを活用した患者とのコミュニケーションが可能となる．このような判断とその理由を，患者や家族に説明し，疑問や不安に耳を傾け，必要に応じて診療記録に残しておく態度が，これからの臨床家には期待されるであろう．

中京大学法科大学院の稲葉一人教授は「診療ガイドラインは患者と医療者の情報共有の基点であり，コミュニケーションの有用なツール」となる可能性を指摘している．稲葉氏は，医療者と患者が診療ガイドラインの信頼性と限界，その役割を知り，医療者は責任と倫理を踏まえて患者の陥りやすい問題を把握し，診療ガイドラインを用いて対話的に治療方針を決める調和的な医療モデルを提案している．意思決定の選択肢が複数ある場合（最良の方法を決めるための確かな情報が無い，不確実性が高い）では，患者と医療者の間で客観的なエビデンスを診療ガイドラインで共有した上で，双方の固有の情報を伝え合うコミュニケーションに基づく“shared decision-making”の必要性が高まっていく．

5. shared decision-making（共有決定）とは？

shared decision-makingは協働的意思決定，協調型意思決定，患者参加型医療などと呼ばれるが，定まった日本語訳は無い．本稿ではsharedの意味を重視して仮に「共有決定」とする．共有決定については以下のような説明がある．

「私はたとえ病気になっても，理性を持つ自律的な人間でありたいと思う．医師は，その力(法律としての，そして知識としての）を患者の苦痛を和らげるためだけに使うのではなく，患者の自律性を強めるために使うべきである．この問題に対する処方せんがshared decision-makingであろう．それは『経験のある者が最善の知識

リスク	高い確実性（最良の選択肢が一つ）	不確実（2つ以上の代替案あり）
高い	A 領域：高いリスク，高い確実性 同意の型：インフォームド・コンセント 共有決定：無し 相互作用：中間．適切に情報を提供された上での決定（informed decision）に十分である程度． 例：腹部銃創に対する腹腔手術	B 領域：高いリスク，低い確実性 同意の型：インフォームド・コンセント 共有決定：あり 相互作用：患者の価値観，選好，希望や恐れについての十分な話し合いを含む． 例：早期乳がんに対する拡大乳房切除術か乳房温存術＋放射線治療
低い	C 領域：低いリスク，高い確実性 同意の型：シンプル・コンセント 共有決定：無し 相互作用：最小限か無し 例：低カリウム血症の患者における利尿薬の減量	D 領域：低いリスク，低い確実性 同意の型：シンプル・コンセント 共有決定：あり 相互作用：中間 例：高脂血症に対する生活習慣の変容と薬物療法

図．shared decision-making（共有決定）の位置づけ
（Whitney SN, et al. A typology of shared decision-making, informed consent, and simple consent. Ann Intern Med. 2004 Jan 6；140（1）：54-9.）

を持っている』というパターナリズムと，急進的な消費者主義の中間にあり，専門家の力とインフォームド・チョイスを調和させる目的を持つ一つの理想である」（Godolphin W, BMJ 2003）

図に臨床の場での意思決定のタイプと共有決定の位置づけを紹介する．共有決定は不確実性の高い場合，すなわち選択肢が複数存在して最良の一つに絞りきれない状況で生じる．表中の「交互作用」は“interaction”の訳であるが，患者と医療者の間で行われるコミュニケーションの特性と言える．

B領域の乳がん治療に際しては，拡大乳房切除術か乳房温存術に放射線治療を追加する方法が選択肢となるであろう．生命予後はほとんど差が無く，どちらを選ぶかは患者本人の価値観に拠ることになる．再発の不安を一掃するために乳房切除を希望する女性もいれば，自分のセクシュアリティやボディ・イメージを大切に思う女性もいる．多くの女性にとって，治療の費用や通院の便利さ，仕事を離れなければいけない時間なども考慮の要因となる．このように治療の有効性がほぼ同様の場合は，患者である女性自身が，自分の気持ちや置かれた状況に対して納得できる決定を行うことが良いであろう．このような場合，患者の女性が十分思慮深く意思決定を行えるように，主治医は適切な情報と助言を提供し，その価値観を尊重して，患者を支援することが望まれる．

D領域の例では，高コレステロール血症と診断された男性が，生活習慣の修正の徹底とコレステロール降下薬の服用という選択肢を持つ場合が考えられる．この場合，生命に対する直接のリスクは乳がんの場合ほど高くは無いが，複数の選択肢がある点で乳がんと同様に「共有決定」が考慮される状況にある．

出生前診断として行う羊水検査は医学的な不確実さという点ではBまたはD領域であり，患者（この場合は両親）の価値観が非常に重要となる．選択は両親の宗教的，道徳的，哲学的な信念によって変わるであろう．選択肢について両親と医療者と十分話し合った後，決定は両親自身が行うように勧めることが望ましいとされている．