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ORIGINAL RESEARCH

Towards a Better Implementation of Treat-to-Target Strategy in Rheumatoid Arthritis: A Comparison of Two Real-World Cohorts

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ABSTRACT

Introduction: Treat-to-target (T2T) strategy has been the core of rheumatoid arthritis (RA) management for over a decade, although it implementation has varied distinctly in real practices. We report here our investigation of the differences in disease activity and target achievement of two patient cohorts with different T2T implementations.

Methods: Data of the CENTRA (Collaboratively intENsive Treat-to-target in RA) and TARRA (Treat-to-TARget in RA) cohorts were used. The CENTRA cohort is a RA cohort prospectively followed up by a fixed team with tight control, while the TARRA is a longitudinal observational cohort followed up by a rheumatologist with casual control. Patients from the two cohorts were matched 1:3 by propensity score matching. The primary outcome was the Simplified Disease Activity Index (SDAI) at the 1-year follow-up.

Results: Included in this analysis were 102 patients from the CENTRA cohort and 271 patients from the TARRA cohort. Both groups were comparable in terms of age, gender, disease course, and seropositivity. At the end of the 1-year follow-up, the SDAI of patients in the CENTRA cohort was significantly lower than that of patients in the TARRA cohort (2.1 vs. 3.4; $p < 0.001$). A similar result was obtained based on the generalized estimating equation (GEE) model ($p = 0.009$). In addition, more patients in the CENTRA cohort achieved SDAI-defined remission compared to the TARRA cohort [72 (70.6%) vs. 134 (49.4%); $p < 0.001$].

Conclusion: Patients with RA may benefit more from a tight control T2T strategy with closer follow-up and appropriate education compared with those with a casual T2T strategy.

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Keywords: Rheumatoid arthritis; Treat-to-target strategy; Disease activity; Follow-up interval; Tight-control

Key Summary Points

Why carry out this study?

The treat-to-target (T2T) strategy has substantially improved the prognosis of patients with rheumatoid arthritis (RA) .

However, implementation of T2T strategies differs in real-world clinical practice, contributing to a significant proportion of patients with RA failing to achieve remission or low disease activity.

What was learned from this study?

Different implementations of T2T strategy have an influence on disease activity in patients with RA.

Patients with RA may benefit more from a tight control T2T strategy with closer follow-up and appropriate education compared with a casual T2T strategy.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with a substantial burden of functional disability. It is a major public health challenge, with almost 20 million prevalent cases globally [1]. During the past decade, the advances in the therapeutic landscape of RA, especially the treat-to-target (T2T) strategy, have substantially improved the prognosis of patients [2, 3]. Both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) recommendations have incorporated T2T strategy as the core of RA management [4, 5]. In recent years, real-world studies have confirmed a higher remission rate and better quality of life in patients who followed a T2T strategy compared to routine care [6, 7]. In addition to these well-known clinical, functional, and structural outcomes, the benefits of the T2T strategy have also been demonstrated in terms of maintaining the ability to work and reducing comorbidities [8].

Since 2010, the treatment target has been specified as clinical remission or alternatively as low disease activity (LDA), assessed by composite disease activity scores. When the specified target is not achieved, adjustment of therapy is recommended [2]. In addition to targeting clinical remission or LDA, close monitoring is also the keystone of T2T strategy implementation, which requires frequent visits to the clinic and good adherence to treatment [9, 10]. Insufficient adherence appears to be an important factor hampering the T2T implementation, resulting in increased disease activity and flares [11–14]. In real-world clinical practice, however, the approaches to the implementation T2T strategies differ, which contributes to a significant proportion of patients with RA failing to achieve remission or LDA [15]. A recent cross-sectional survey that included 30,501 Chinese patients with RA revealed that approximately 80% patients had moderate or high disease activity (MDA/HDA) [16]. However, in our Treat-to-TARget in RA (TARRA) cohort, 80% of the patients with RA reached LDA or remission defined by both the mean and time-adjusted Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) during 8 years of follow-up [6]. The significant difference in reaching the target reflects the substantial variations in T2T implementation in different practices, and triggered us to analyze the difference in disease activity based on two real-world RA observational cohorts we have established based on different T2T implementation.

METHODS

Setting

Cohorts

Data from two cohorts at our center were analyzed. The TARRA cohort is a longitudinal observational retrospective RA cohort that has

Table 1 Critical characteristics in the unmatched and propensity score-matched cohorts

Critical patient characteristics	Unmatched cohort			Matched cohort		
	TARRA cohort (n = 389)	CENTRA cohort (n = 111)	p value	TARRA cohort (n = 271)	CENTRA cohort (n = 102)	p value
Basic characteristics						
Age, mean (SD), years	56 (17)	53 (17)	0.026	52 (13)	50 (13)	0.114
Male gender, n (%)	77 (19.8)	24 (21.6)	0.672	59 (21.8)	21 (20.6)	0.804
Disease duration, mean (SD), months	18 (66)	49 (108)	0.000	24 (90)	37 (85)	0.064
Positive RF, n (%)	289 (74.3)	92 (82.9)	0.061	220 (81.2)	83 (81.4)	0.966
Positive Anti-CCP, n (%)	330 (84.8)	98 (88.3)	0.360	246 (90.8)	89 (87.3)	0.316
Initial therapy						
MTX, n (%)	313 (80.5)	94 (84.7)	0.313	220 (81.2)	87 (85.3)	0.353
LEF, n (%)	198 (50.9)	29 (26.1)	< 0.001	133 (49.1)	25 (24.5)	< 0.001
Combination of DMARDs, n (%)	148 (38)	20 (18)	< 0.001	100 (36.9)	17 (16.7)	< 0.001
Glucocorticoids, n (%)	101 (26)	12 (10.8)	< 0.001	65 (24)	10 (9.8)	0.002
Biological/targeted DMARDs during follow-up, n (%)						
	13 (3.3)	11 (9.9)	0.004	9 (3.3)	8 (7.8)	0.062
Disease activity scores at baseline, median (IQR)						
DAS28	4.2 (2.1)	3.7 (2.5)	0.047	4 (2.1)	3.8 (2.5)	0.564
CDAI	14 (14.5)	11 (15)	0.026	12 (14)	11 (15.3)	0.259
SDAI	14.5 (14.9)	11.7 (15.7)	0.018	13.1 (13.1)	11.9 (16)	0.226

CCP Cyclic citrullinated peptides, *CDAI* Clinical Disease Activity Index, *DAS28* 28-Joint Disease Activity Score, *DMARDs* disease-modifying anti-rheumatic drugs, *IQR* inter-quartile range, *LEF* leflunomide, *MTX* methotrexate), *RF* Rheumatoid factor, *SD* standard deviation, *SDAI* Simplified Disease Activity Index

been established for over a decade. Details on this cohort are reported in our earlier studies [6, 17]. The CENTRA (Collaboratively intENsive Treat-to-target in RA) cohort is a prospective cohort set up in October 2015.

In both the TARRA and CENTRA cohorts, the management of patients with RA has been based on the concept of T2T. The target is either CDAI- or SDAI-defined remission or LDA. In both cohorts, we assess the disease activity at each visit and make decisions on treatment and the interval to next visit accordingly. Frequency of follow-up is mostly determined by the disease activity, monthly for those patients with active disease, and every 3–6 months for those with target achievement. There is no predefined treatment protocol for the patients in both cohorts, but we do follow the principles of the EULAR recommendations for the application of disease-modifying anti-rheumatic drugs (DMARDs) [18]. If the goal has not been reached at the clinic visit, we proceed to increase the

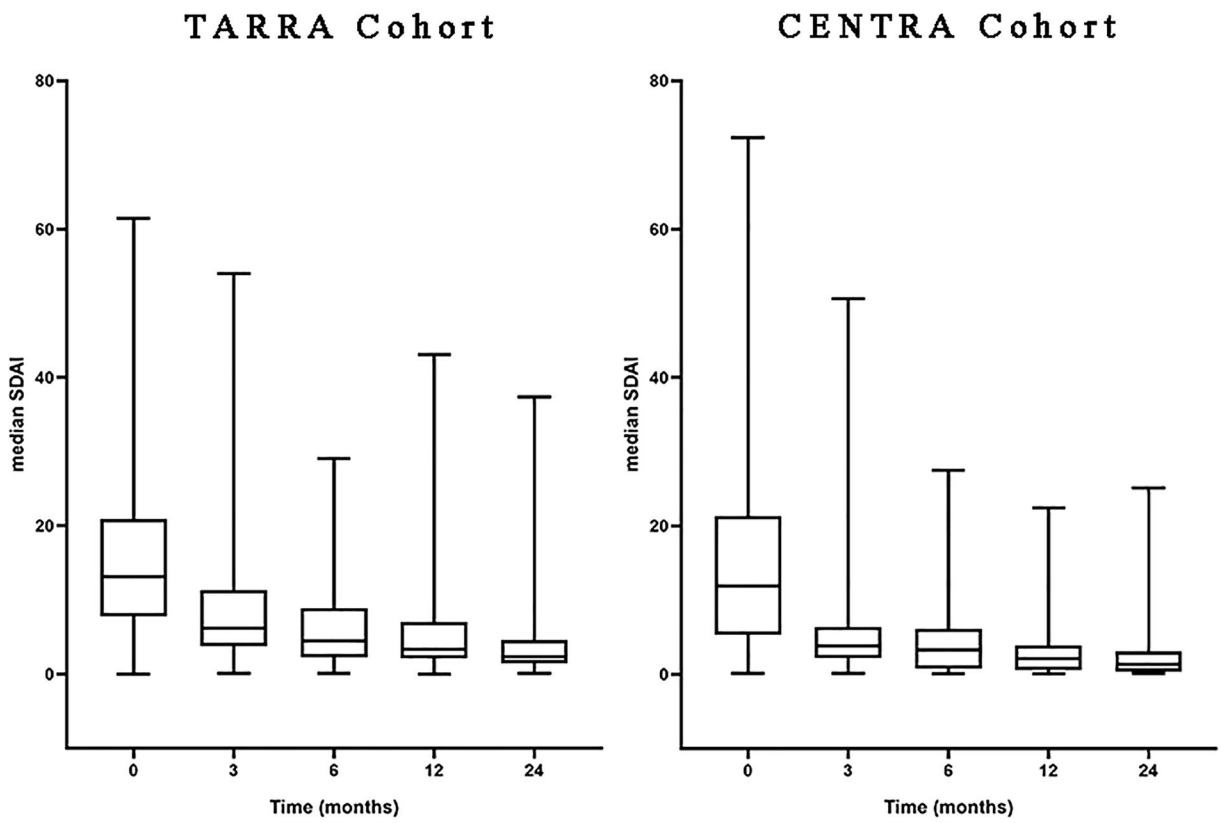

Fig. 1 Trends in disease activity scores according to Simplified Disease Activity Index (*SDAI*) over 2 years in the TARRA cohort and CENTRA cohorts

therapy with aim of achieving the treatment goal at the next visit.

The major disparities in the management of patients in the two cohorts are as follows. (1) In the TARRA cohort, all patient care was provided by a treating rheumatologist, while in CENTRA cohort, all assessments are conducted by a fixed team consisting of a group of rheumatologists and a specially trained nurse. (2) In the TARRA cohort, at the end of each visit, a time frame for the next visit is suggested, but there is no fixed appointment. In the CENTRA cohort, the follow-up visits are pre-scheduled at every 3 months for the first year and then every 6 months if remission or LDA is achieved. Patients are always given an appointment for the next visit, and the nurse will remind each patient of his visit appointment 1 week before the upcoming visit. Additional visits will be arranged if needed. (3) In the TARRA cohort, at each visit the disease activity scores were calculated, while in the CENTRA cohort, additional assessments are performed, including patient-reported outcomes and musculoskeletal ultrasound. Radiographs of the hands and feet and bone mineral density and carotid ultrasounds are arranged at baseline, year 1 of treatment, and then at 2-year intervals. (4) The CENTRA cohort received patient education, either face-to-face or by webinar, at least twice a year on the disease, medications, and guidance for home-based exercise. In comparison, very limited patient education is provided for the patients in the TARRA cohort due to the very heavy clinical workload.

Accordingly, the TARRA cohort is referred to as the 'casual T2T cohort' hereafter and the CENTRA cohort as the 'collaboratively tight-control T2T cohort.'

Table 2 SDAI scores of the two cohorts during follow-up

Time point during follow-up	Unmatched cohort					Matched cohort				
	TARRA cohort (n = 389 at baseline)		CENTRA cohort (n = 111 at baseline)		p value	TARRA cohort (n = 271 at baseline)		CENTRA cohort (n = 102 at baseline)		p value
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	
SDAI at 3 months	343	6.2 (8)	106	4.2 (5)	< 0.001	241	6.2 (7.6)	97	3.8 (4.2)	< 0.001
SDAI at 6 months	365	4.4 (6)	102	3.3 (5.2)	0.002	253	4.5 (6.7)	93	3.3 (5.4)	0.001
SDAI at 12 months	389	3.2 (5)	111	2.2 (4.5)	< 0.001	271	3.4 (4.9)	102	2.1 (3.4)	< 0.001
SDAI at 24 months	283	2.4 (3.2)	67	1.4 (3.4)	0.004	185	2.3 (3.1)	62	1.3 (2.8)	0.004

The data recorded for both cohorts include age, sex, disease duration, body mass index, current and past smoking status, menopausal status, and past medical history. Components of the Disease Activity Score based on 28 joints [DAS28; tender joint count (28-TJC) and swollen joint count [28-SJC]), patient's global assessment (PGA; Visual Analog Scale [VAS] for Pain measured along a 100-mm line [100-mm VAS]), evaluator's global assessment (EGA; 100-mm VAS), and questionnaires concerning patient-reported outcomes are performed at baseline and at all follow-up visits. Disease activity scores based on DAS28 and erythrocyte sedimentation rate (DAS28-ESR), disease activity scores based on DAS28 and C-reactive protein (DAS28-CRP), SDAI, and CDAI are calculated to assess the disease activity.

Complete blood count, hepatic and renal function, ESR (mm/h), CRP (mg/L), and rheumatoid factor (RF, IU/ml) are routinely tested at each visit. Anti-cyclic citrullinated peptides (anti-CCP, RU/ml) and anti-mutated citrullinated vimentin (anti-MCV, U/ml) are tested at baseline, year 1 of treatment, and then at 1-year intervals. DMARDs used at baseline were recorded, including conventional synthetic DMARDs [csDMARDs; e.g., methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ), sulfasalazine (SSZ), glucocorticosteroids (GC)] and biological/targeted synthetic DMARDs (b/tsDMARDs). The prescribed GC dose was converted to prednisolone equivalent dose and the data collected as a cumulative dose during follow-up.

Participants

The TARRA and CENTRA cohorts included adult patients who fulfilled the 2010 ACR/EULAR classification criteria for RA. [19] We obtained the data on patients in the TARRA cohort between 2009 and 2015, and on patients in the CENTRA cohort between 2015 and 2019. The participants chosen for this study must have attended at least three visits during follow-up without being absent for more than 12 months between consecutive visits, with a minimum follow-up of 1 year. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments and approved by the Ethics Committee of Peking University First Hospital. Informed consent was obtained from each patient.

Data Collection

Variables collected and included in this comparative analysis were age, gender, disease duration, 28-SJC and 28-TJC, ESR, CRP, RF, anti-CCP, PGA, EGA, and treatment details. The formula used to calculate the composite disease activity scores with corresponding definitions of remission and LDA are as following [20–22]:

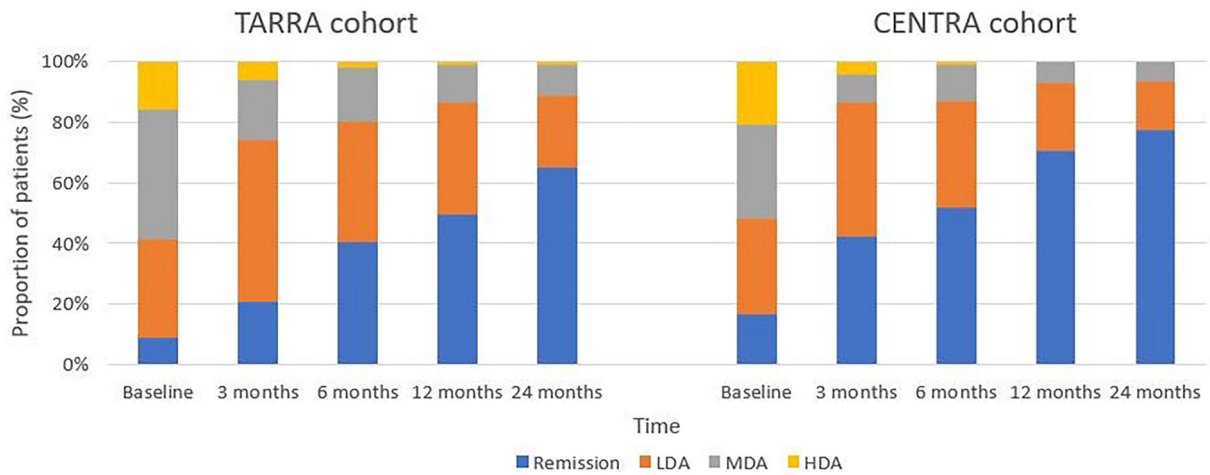

Fig. 2 Trends in the percentage of remission, low, moderate and high disease activity (*LDA*, *MDA*, *HDA*, respectively) during the 2-year follow-up by SDAI in the TARRA and CENTRA cohorts

CDAI = (TJC28 + SJC28 + PGA + EGA) $\leq$ 2.8 (remission); > 2.8 and $\leq$ 10 (LDA)
SDAI = (TJC28 + SJC28 + CRP + PGA + EGA) $\leq$ 3.3 (remission); > 3.3 and $\leq$ 11 (LDA)
DAS28-ESR = (0.56 $\sqrt{}$[TJC28] + 0.28 $\sqrt{}$[SJC28]+0.7 × ln[ESR] + 0.014 × PGA) < 2.6 (remission); $\geq$ 2.6 and $\leq$ 3.2 (LDA)

SDAI at the 1-year follow-up was defined as the primary outcome of this study. Secondary outcomes included the SDAI at the remaining time points (i.e., 3 months, 6 months, and 2 years), as well as the corresponding CDAI and DAS28, and the proportion of patients in SDAI-/CDAI-/DAS28-defined remission/LDA/MDA/HDA. We also analyzed and compared the frequency of visits when remission was reached and not reached, respectively.

Statistical Analysis

All descriptive statistics are presented as means and standard deviations, and/or medians and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. For continuous variables, independent *t* tests or non-parametric tests were applied. Comparison of categorical data was performed using Chi-square tests. The Propensity Score Matching (PSM) method was used with SPSS version 3.0.4 software (SPSS IBM Corp., Armonk, NY, USA. A value for each patient was calculated based on the covariates of gender, age, disease duration, RF, anti-CCP, and SDAI at baseline, following which patients in the CENTRA cohort and TARRA cohort were matched with a 1:3 ratio considering a caliper = 0.1.

Frequency of visits was evaluated for each patient in both cohorts during the follow-up intervals when remission was reached and not reached, respectively. We took into account the impact of the coronavirus pandemic and used the data before 2020 in the CENTRA cohort.

The trend of disease activity was analyzed using generalized estimating equations (GEE) with a robust estimation for the covariance matrix. All reported *p* values are two-sided, and $p < 0.05$ is considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS IBM Corp.).

RESULTS

Patient Characteristics

Initially 389 patients in the TARRA cohort and 111 patients in the CENTRA cohort were included in the study. After 1:3 PSM for age, gender, disease duration, positive RF, positive

anti-CCP, and SDAI at baseline, 271 patients in the TARRA cohort and 102 patients in the CENTRA cohort were ultimately enrolled in this study. At baseline, 39.8% (108/271) and 43.1% (44/102) of patients in the TARRA and CENTRA cohorts, respectively were DMARD-naive. In total, patients in the TARRA cohort completed 986 visits, with a median follow-up interval of 4.3 months when they reached SDAI-defined remission and 1438 visits and 3.3 months, respectively, when they did not reach remission. Correspondingly, patients in the CENTRA cohort completed 420 visits, with a median follow-up interval of 4.3 months when they reached SDAI-defined remission, and 339 visits and 3.1 months, respectively, when they did not reach remission. Differences between the TARRA and CENTRA cohorts are as follows: percentage of males (21.8 vs. 20.6%), mean age (52 ± 13 vs. 50 ± 13 years), disease duration (24 ± 90 vs. 37 ± 85 months), positive RF (81.2 vs. 81.4%), and anti-CCP (90.8 vs. 87.3%) (Table 1).

Disparities in Treatments of the Two Patient Cohorts

In terms of initial treatment, MTX was equally most often used in both cohorts [220 (81.2%) in TARRA vs. 87 (85.3%) in CENTRA]. However, LEF, DMARD combinations, and GC were more frequently used in the TARRA cohort compared to the CENTRA cohort [133 (49.1%) vs. 25 (24.5%); 100 (36.9%) vs. 17 (16.7%); 65 (24%) vs. 10 (9.8%), respectively]. In the CENTRA cohort, 21.6% (22/102) of patients had ever been exposed to GC, compared to 30.3% (82/271) of patients in the TARRA cohort ($p = 0.12$). The median (IQR) cumulative dose of prednisone was 1462.5 (763.1) mg and 2305.0 (1422.5) mg in CENTRA and TARRA cohorts, respectively ($p < 0.001$). During follow-up, nine (3.3%) and eight (7.8%) patients in the TARRA and CENTRA cohorts, respectively, received b/tsDMARDs therapy ($p = 0.062$).

Disparities in Disease Activity of Two Cohorts

Disease activity of the patients in two cohorts during follow-up is summarized in Table 2 (SDAI) and in Electronic Supplementary Material (ESM) Table S1 (CDAI and DAS28). Overall, there was a steady decrease in disease activity based on the SDAI, CADI and DAS28 in two cohorts throughout the follow-up [see Fig. 1 (SDAI) and ESM Fig. S1 (CDAI and DAS28). Compared to the TARRA cohort, the SDAI of patients in the CENTRA cohort was significantly lower at the end of first year (3.4 vs 2.1; $p < 0.001$). Similar results were observed for the disease activity measured by CDAI and DAS28, as well as at other follow-up time points (months 3, 6, and 24).

At the end of the 1-year follow-up, the SDAI of patients in the CENTRA cohort was also significantly lower than that of the TARRA cohort based on the GEE model ($p = 0.009$). In addition, more patients in the CENTRA cohort than in the TARRA cohort achieved SDAI-defined remission [72 (70.6%) vs. 134 (49.4%); $p < 0.001$]. The trend in disease activity of patients from both cohorts during follow-up is shown in Fig. 2 (SDAI) and ESM Fig. S2 (CDAI and DAS28).

DISCUSSION

T2T strategy was first introduced into RA management in 2010 [2]. Several randomized controlled trials have proved the significant value of the T2T strategy, and it has been accepted as the basis of all current guidelines and recommendations [23]. Nevertheless, the T2T strategy has been implemented in distinctly varied ways, with the result that many patients with RA continue to have MDA or HDA in real-world practice [3, 24, 25]. In this study, we investigated the difference in disease activity in two cohort of patients under different management scenarios, although both are referred to as T2T strategies. The major differences between the two cohorts lie in the manner in which each T2T strategy was implemented, which also reflects real practices in the T2T era.

Importantly, we found that disease activity was significantly lower in the CENTRA cohort than in the TARRA cohort, with more patients in the former cohort achieving remission during follow-up. Based on our findings, we advocate an approach for managing patients with RA that involves just with a little more effort.

A key challenge for T2T implementation is that insufficient monitoring results in reduced target achievement. One of the major reasons for failure of tight control has been low follow-up frequency. For those patients who had not reached remission in this study, we found that the intervals between visits were shorter for patients in the CENTRA cohort than for those in the TARRA cohort. This finding re-emphasizes the importance of closer follow-ups. Patients in the CENTRA cohort will always receive telephone reminders of appointment dates and examinations before each visit by the nurse. This has played a vital role in tight control, leading to superior disease activity control, with more patients who achieved remission at the end of first year of follow-up. The role of specialist nurses in patient follow-up has been highlighted in the EULAR recommendations for the management of RA [23]. But to date, nurses rarely participate in the follow-up and assessment of patients with RA in rheumatology clinics in China.

A successful T2T approach also requires shared decision-making by clinicians and patients. Enlisting patients as partners is an important principle of T2T. An increased willingness of patients to comply with their treatment regimen is associated with lower disease activity and better functional outcomes [13, 26, 27]. Appropriate patient education, self-management skills, and belief in their ability to manage the disease are essential to achieving the treatment goal [28]. In addition to face-to-face consultations, the patients in the CENTRA cohort also benefit from various education programs, including webinars and educational videos. These programs have helped patients to improve their disease awareness and treatment compliance.

We are aware that our study has a number of limitations of the study. First, the recruitment period of patients in the two cohorts was different. The clinical evolution of the disease may have been influenced by new medications having become available as well by as other factors due to different recruitment time of patients in the two cohorts. The cumulative dose of prednisone was higher in the TARRA cohort than in the CENTRA cohort. In the past, we used more GC, as reported in our previous study [17]. However, in T2T, the strategies are more important than the medications. A good example is the BeSt study, in which over 80% of patients with RA from each of the four groups reached the target regardless of the therapeutic algorithm [29]. In China, tumor necrosis factor inhibitors were launched in 2007, and these are now more commonly used (2009–2019). The first Janus kinase (JAK) inhibitor was launched in 2017, but only very occasionally used before 2020 due to the high price. Therefore, new therapy seemed not to be a very important factor affecting the evolution of disease reported in these two cohorts. Moreover, we adopted the PSM method to eliminate the imbalance of treatment between two cohorts. Second, we did not include radiographic and health assessment questionnaire data in our study, but focused instead on the change in disease activity and target achievement during follow-up in both cohorts. We found that disease activity was lower in patients in the CENTRA cohort than in those in the TARRA cohort. It has been substantially proved that better control of disease activity is associated with less joint damage and disability, and the fulfillment of clinical remission was definitely associated with the increased possibility of functional remission [30–32]. We can deduce that patients in the CENTRA cohort should benefit more than patients in TARRA cohort. In the current T2T strategies, remission or LDA remains the treatment goal, although perusing radiographic non-progression and high quality of life is the ultimate goal.

CONCLUSIONS

Although T2T strategy has been ingrained into the management of patients with RA, the implementation still needs improvement. Our study involving two cohorts of patients with RA

with varied T2T implementations further corroborates the management of tight control with closer follow-up and appropriate education providing favorable outcomes.

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Author contributions. ZZ conceived of the study, participated in its design and critically revised the manuscript. HH had full access to all the data collection, analysis, interpretation, and drafted the manuscript. WX, YG, YF YW and JZ were study investigators and contributed to the process of data collection. All authors read and approved the final manuscript.

Disclosures. Hong Huang, Wenhui Xie, Yan Geng, Yong Fan, Yu Wang, Juan Zhao and Zhuoli Zhang have nothing to disclose.

Compliance with ethics guidelines. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments and approved by the ethics committee of Peking University First Hospital. Informed consent was obtained from each patient.

Data availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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