Trends in the activity of rheumatoid arthritis as the consequence of treat-to-target strategy: eight-year data from 2009 to 2016

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Abstract

Objective

To investigate the trends in the activity of rheumatoid arthritis (RA) over the past 8 years and evaluate the value of treat-to target (T2T) strategy in daily practice.

Methods

All the medical records of RA patients from 2009 to 2016 were retrospectively reviewed. Disease activity scores at obtained visits were measured by DAS28-CRP, DAS28-ESR, SDAI and CDAI. To display trends over years, both mean and time-adjusted methods were applied in calculation of annual disease activity and remission rate. Disease activity and remission rate were also compared before and after the year 2011 when application of T2T strategy was initiated in our centre. Furthermore, a sub-cohort study including T2T and non-T2T period groups was conducted with outcome of cumulative percentage of remission and time to achieve first remission during the first year follow-up.

Results

In total, 1,001 patients with 6,944 clinical visits were included. Over an eight-year period, significant improvements were witnessed in disease activity and remission rate, measured by all four indices ($p<0.0001$). More patients achieved lower disease activity and higher remission rates after T2T adherence in 2011 compared to those in the years 2009 and 2010 ($p<0.0001$). Moreover, sub-cohort study revealed that more patients (49.3–73.2% vs. 19.1–34.5%, OR=2.4–3.0) achieved remission with a shorter median time compared with the non-T2T period group ($p<0.0001$), particularly in DAS28-CRP (21 vs. >52 weeks), DAS28-ESR (37 vs. >52 weeks).

Conclusion

Over the past 8 years, the RA activity has substantially decreased and T2T strategy was directly attributable to the favourable changes in clinical practice.

Key words

rheumatoid arthritis, treat-to-target, disease activity, remission, trends

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Received on November 26, 2017; accepted in revised form on January 31, 2018.

Funding: this work was supported by sub-project (2010CB529103) under the National Science Technology Pillar Program of China (973 Program) (2010CB529100), the Capital Health Research and Development of Special Fund Program (2011-4021-03) and the Peking University Clinical Research Program (PUCRP201305).

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterised by persistent synovitis, subsequent bone erosion and disability. RA affects up to 1% of population worldwide and approximately 0.36% in Chinese populations (1-3). A nationwide investigation in 2006 showed that RA was the leading reason of female disability in China (4). Therefore, better control of disease activity is imperative to improve the outcome of RA.

Unquestionably, the outcome for RA patients has been dramatically improved in the past decades, driven largely by the advent of new medications (particularly biological agents) as well as the strategies of early treatment and treat-to-target (T2T) treatment. T2T strategy aiming at clinical remission or alternatively low disease activity (LDA) has been gradually applied in clinical practice since 2010 and its value has been strongly proved by extensive clinical trials (5, 6) and observational studies (7-10) in the past years. Compared with the conventional care, T2T strategy can considerably lower disease activity, improve remission rate, slow the progression of joint damage, and finally result in a better clinical outcome.

A state of clinical remission is generally defined as disease activity score in 28 joints using C-reactive protein level (DAS28-CRP) ≤2.6, disease activity score in 28 joints using erythrocyte sedimentation rate level (DAS28-ESR)≤2.6, the simplified disease activity index (SDAI)≤3.3, the clinical disease activity index (CDAI)≤2.8. Previous cross-sectional studies have shown the remission rates in RA patients was about 4.5-49% over the last decade based on aforementioned indices (11-14), but data from large population aiming at reflecting such trends in the activity and remission of RA over past years are grossly inadequate.

Besides, several nationwide surveys indicated that less than half physicians implemented this strategy in their daily practice because of insufficient confidence or other reasons. In many finished research projects, the efficacy of T2T was verified based on relatively ideal clinical setting (15-17). Whether the treatment approach is also effective in real-life clinical practice needs to be validated further. Therefore, we set out to outline the trends of RA disease activity and remission rate over the past eight years and investigate the efficacy of T2T in a real clinical setting at a single centre in China from 2009 to 2016.

Materials and methods

Section 1

Study population

The present study was conducted at a tertiary university hospital and approved by the institutional Research Ethics Committee. All patients consented to data collection from their medical records. Medical records between January 1, 2009 and December 31, 2016 were retrospectively reviewed by two rheumatologists for all patients with definite diagnosis of RA according to the 1987 American College of Rheumatology (ACR) classification Criteria (18) or 2010 ACR/European League Against Rheumatism (EULAR) rheumatoid arthritis classification criteria (19). To ensure data accuracy, a third rheumatologist was involved when there was any discrepancy in the judgement of data between the two rheumatologists. The inclusion criteria were adults (≥18 years), at least 3 visits to our centre without being absent for more than 12 months between consecutive visits. Patients with other connective tissue diseases (except Sjögren's syndrome without hypergammaglobulinaemia) or diseases exerting obvious influence on inflammatory markers, for instance, monoclonal gammopathy of undetermined significance, POEMS syndrome, were excluded in the study. Data at certain distorted visits when some temporary situations (e.g. acute infection, fracture, and trauma) with obvious influence on the assessment of RA, especially serological inflammatory markers occurred were discarded.

Data collection and analysis

All data were obtained from medical records. Data collected included: (1) demographics: sex, age; (2) clinical features of RA: duration of disease, tender joint counts (TJC28) and swollen joint

counts based on 28 joints (SJC28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), titres of rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti-CCP), patient's global assessment (PGA), evaluator's global assessment (EGA), and (3) initial treatment with disease-modifying anti-rheumatic drugs (DMARDs), for instance, methotrexate (MTX) , hydroxychloroquine (HCQ), leflunomide (LEF), sulfasalazine (SSZ) as well as glucocorticoids (GCs) (including oral, intravenous, intramuscular and intraarticular administration of prednisone and other compounds). The use of biological agents was recorded throughout the whole study periods. Early stage RA was defined when the duration from onset of first arthritic symptom to the first visiting in our centre with definite diagnosis of RA was no more than one year. A patient who never received DMARDs treatment or was on DMARDs treatment for less than 3 months before visiting our centre was defined as a treatment-naive patient.

All obtained data from records at each visit was retrospectively analysed. Calculating disease activity score and remission status for all visits were in accordance of DAS28-CRP, DAS28-ESR, SDAI and CDAI. Then mean method and time-adjusted (AM) mean method (see below) were applied to compute annual disease activity scores and remission rates. Finally, the secular trends toward annual diseases activity score and remission rate over 8 years were depicted and the changes before and after T2T were displayed. Notably, taking the timing of T2T release and application in our department into account, we defined the year of 2011 as a boundary of T2T application in the study. Namely, our department has been complying with the T2T strategy since Jan 1, 2011. We usually follow up tightly our patients in remission already every 3–12 months and patients who have not reached in remission more frequently at every 3 months. Besides, an explicit goal of achieving remission was set and appropriate treatment adjustments were based upon disease activity scores and musculoskeletal ultrasonic manifestations.

• *Calculation of disease activity scores and definitions of remission*

Currently, a variety of validated instruments were available to score disease activity for RA patients. Some of them are relatively loose while some are relatively stringent, but there is still no universal consensus on the assessment of disease activity and remission. In this way, the calculation for disease activity and definition of remission at each visit according to the following definitions and formula:

(1) DAS28-CRP=(0.56√[TJC28]+0.28√[SJC28] +In[ESR]+0.014×PGA) ≤2.6

(2) DAS28-ESR=(0.56√[TJC28]+ 0.28√[SJC28] +In[CRP+1]+0.014×PGA+0.96) ≤2.6

(3) SDAI=(TJC28+SJC28+CRP+PGA+EGA) ≤3.3

(4) CDAI=(TJC28+SJC28+PGA+EGA) ≤2.8

• *Annual disease activity score and remission rate*

To our understanding, there is no universally accepted approach to summarising disease activity over multiple visits covering years of follow-up. Based on some related literature, the mean method and adjusted mean method were applied to character these data (20-25). In this way, each patient had only one mean or adjusted mean value of disease activity score per year to mirror his annual disease activity.

• *Mean disease activity*

Calculating a mean is a common method to reflect changes in disease activity over multiple visits, and can provide the best fit to clinical trials with rather regular follow-up interval. Precisely, disease activity scores and remission status derived from each visit for patients was averaged annually (for example, for a patient who visited our clinic 4 times in 2011, the average value of 4 visits represented his disease activity in 2011). All the patients had their mean values per year.

• *Time-adjusted mean disease activity*

Running under our national healthcare system, satisfactory control of the visit interval is usually uneasy because a patient is able to visit the clinic without appointment. There are always some patients who come to clinic more regularly in periods of active disease and return with less frequency in periods of lower activity, while some who come less frequently when disease is more active and return regularly when disease activity is less. Considering the presence of varying time intervals may interfere with the accurate calculation of mean annual disease activity, time-adjusted method was adopted to evaluate the annual disease activity and remission rate. Briefly, the theory of the method is calculating the area under the curve of disease activity over time by adding the area of each of the blocks of visit interval and then dividing them by the length of time for the whole period. The strengths of adjusted-mean are easy to calculate, more objective and not restrained by different time interval. The changes in annual disease activity and remission rate were presented in the similar manner throughout 8 years.

Section 2

Sub-cohorts study

In an attempt to minimise the potential accumulative influence of long-term follow-up on the effect of T2T strategy, we selected those patients who were not in remission by all indices at their first visit between 2009 and 2015 and then allocate them into "non-T2T period group" or "T2T period group" according to the time of their first clinic visit prior to or after 2011. To demonstrate the T2T adherence in our centre since 2011, we measured the average number of visit per year in patients with remission/low disease activity (LDA) and moderate/high disease activity (MDA/HDA) in both T2T and non-T2T period groups. Additionally, the regular follow-up was defined when two consecutive visit intervals was no more than 12 months in patients who reached remission/LDA or no longer than 3 months in patients with MDA/HDA. All data was also retrieved and compared between non-T2T and T2T period groups in terms of cumulative percentage of remission and time to achieve first remission during the first year follow-up.

Statistical analysis

The distributions of continuous variables were examined. Normally dis-

tributed continuous variables were presented as means and standard deviations (SDs), while skewed distributed continuous variables were depicted as medians and interquartile ranges (IQRs). Absolute and relative frequencies were reported for categorical variables. Remission rates were calculated based on each of the four definitions, presented as percentages with 95% confidence intervals (95% CIs).

Comparisons of the demographics, clinical characteristics between the two groups were performed by using Student's *t*-tests for normally distributed continuous variables, Mann-Whitney U-tests for skewed continuous variables, and the chi-square tests for categorical variables. Kaplan-Meier survival curves and Cox proportional hazards regression model including confounder correction were performed to analyse the between-group difference in accumulative percentages of remission and time to achieve remission. The trends of disease activity and remission rate over 8 years was analysed using generalised estimating equations (GEE) with an unstructured working correlation matrix and a robust estimation for the covariance matrix. Adjustment for baseline DAS28 in the study was performed systematically for GEE analysis. The level of significance was set at a two-sided *p*-value less than 0.05. All the analyses were conducted using SPSS v. 20.0.

Results

Section 1

Demographics and clinical characteristics of RA patients

Among 1906 consecutive RA patients in our databank from 2009 to 2016, 905 patients were excluded according to the aforementioned criteria (Fig. 1A) and 1,001 patients were eventually included in the analysis. Of 1001 patients, 779 (77.7%) were women, with mean age of 54±14 years and median (IQR) disease duration of 24 (6-84) months. The demographics, baseline clinical features including disease activity and initial therapy of 1001 enrolled patients were shown in Table I. In total of 6,944 clinic visits over study period, data for CDAI, SDAI, DAS28-CRP and DAS28-ESR were respectively available in 100%, 98.7%, 98.7% and 99.1% visits. In the present study, the annual drop-out rate during 8 years ranged between 8.2% and 12.0%.

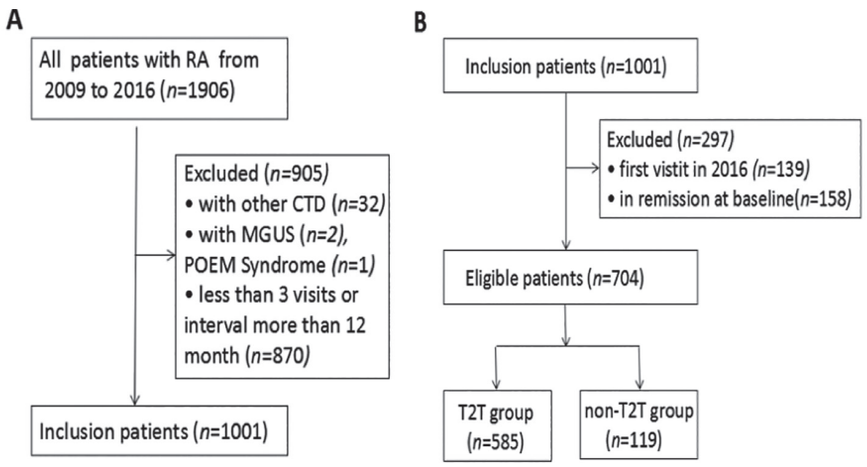

Fig. 1. Flow diagram for the retrospective study. **(A)** Section 1 **(B)** Section 2

Table I. Demographics and clinical characteristics of RA patients.

Characteristics of 1001 RA patients	
Basic characteristics	
Women, n (%)	779 (77.7%)
Age (years)	54 ± 14
Disease duration (months)	24 (6-84)
RF positive, n (%)	770/993 (77.5%)
Anti-CCP positive, n (%)	798/932 (85.6%)
Early stage, n (%)	460 (45.9%)
Treatment-naïve, n (%)	583 (58.1%)
Baseline disease activity measures, median (IQR)	
TJC28	3 (1-7)
SJC28	2 (0-4)
ESR mm/h	28 (14-47)
CRP mg/l	8.04 (3.20-21.93)
PGA, 0-10cm	4.5 (2-6)
EGA, 0-10cm	3 (2-5)
Initial therapy, n (%)	
MTX	798 (79.6%)
LEF	488 (48.7%)
HCQ	372 (37.1%)
SSZ	58 (5.8%)
Glucocorticoids	618 (61.7%)
Biological agents	40 (4.0%)

Values are presented as mean (SD) or median (IQR), as applicable.
SD: standard deviation, IQR: interquartile ranges.

Trend in disease activity

A steady decrease, on the whole, in disease activity based on the DAS28-CRP, DAS28-ESR, SDAI and CADI by using either mean or adjusted mean methods throughout the 8 years was presented in Figure 2. Disease activity scores in 2016 by DAS28-CRP, DAS28-ESR in two methods declined 1.02–1.28 (27–35%) compared with those in 2009 (Fig. 2A). The first three years experienced the noticeable improvement in disease activity with 0.79–0.97 (22–26%) reduction. Similarly, the median SDAI and CDAI by mean and time-adjusted mean methods dropped around 8.5-12.8 (67.4–75.4%), with dramatic fall of 6.0–9.0 (45.9–53.1%) in the first three years (Fig. 2B). Besides, there was a general agreement between the DAS28-CRP and DAS28-ESR, but interestingly the mean and time-adjusted mean DAS28-CRP were always lower than that of DAS28-ESR around 0.3 annually.

Trends in the percentage of remission, low, moderate and high disease activity

A dramatic upward trend was clearly observed regarding the percentage of remission and low disease activity, accompanied by the corresponding decline in moderate and high disease activity from 2009 to 2016 ($p<0.0001$) (Fig. 3). Of note, there was a radical increase in the rate of remission between 2010 and 2011, and by 2016, 62.9% (67.1%), 50.4% (54.3%) of remission rates were attained according to mean (adjusted mean) DAS28-CRP and DAS28-ESR respectively. Although SDAI and CDAI experienced relatively slow rise in remission, the percentages of patients in remission and LDA clearly increased from 2009 to 2016 ($p<0.0001$), especially during 2010 and 2011. Acceptably, 80% of our patients reached LDA or remission defined by both mean and time-adjusted SDAI and CDAI in 2016. This observed discrep-

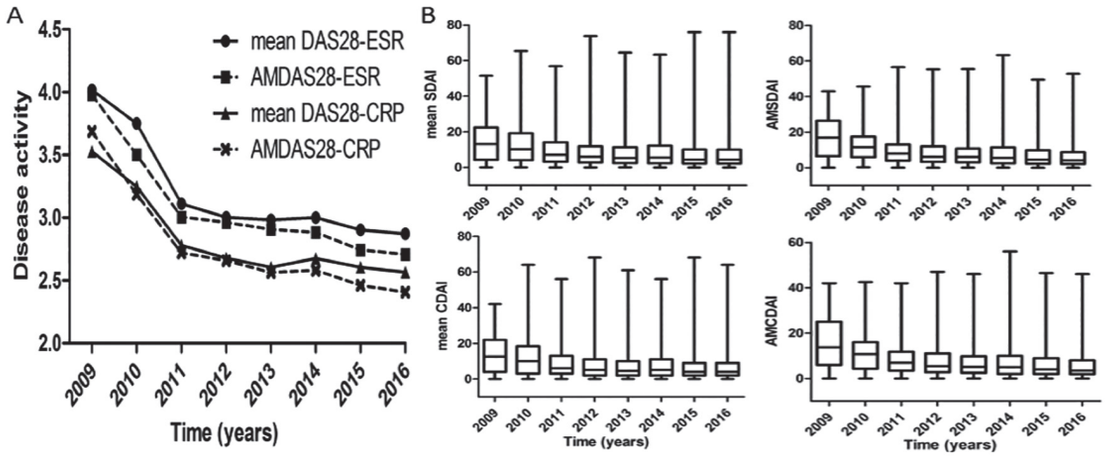

Fig. 2. Trends in disease activity scores over 8 years by four indices in mean and adjusted mean (AM) methods.
A: Trends based on DAS28-CRP and DAS28-ESR in two methods.
B: Trends based on SDAI and CDAI in two methods

Fig. 3. Trends in the percentage of remission, low, moderate and high disease activity over 8 years by four indices in mean and time-adjusted mean (AM) methods.
A: Trends based on mean method; **B**: Trends based on AM method.

ancy among these validated composite measures was consistent with the previous opinion that DAS28-CRP and DAS28-ESR are looser than SDAI and CADI in terms of definition of remission, but DAS28-CRP and DAS28-ESR were nearly in line with SDAI, CDAI for defining LDA.

Changes in the disease activity and remission rate before and after 2011

All the patients were split into two groups according to the time of their first clinic visit prior to 2011 or after 2011. A significant decrease in annual disease activity measured by all composite scores was observed after 2011 compared to before 2011, a time boundary of T2T adherence defined in this study (p<0.0001) (Table II). On the other hand, the annual remission rate based on DAS28-CRP, DAS28-ESR, SDAI and CDAI were compared by applying both of the two methods before and after 2011. Significantly, more patients treated with T2T strategy after 2011 reached remission than those with usual care before 2011 (p<0.0001). Notably, after the institution and adherence of T2T, the annual remission rate in 2011 was in stark contrast with those in 2009 and 2010, with an odd of being approximate 3-times higher (Table III). Thus, these observations highlighted that the emergency of T2T strategy is apparently beneficial to the management of RA patients, resulting in decreasing disease activity, more patients in remission/LDA in daily practice.

Section 2

Baseline features of sub-cohort patients

Seven hundred and four patients who did not reach remission at their first visit between 2009 and 2015 were included in the section of study, and most of inclusion patients had moderate or high

disease activity. 119 of them were allocated into "non-T2T period group" and 585 patients into "T2T period group" according to the time of their first clinic visit prior to 2011 or after 2011 (Figure 1B). The subjects were well balanced in both the two groups of participants in terms of gender distribution, autoantibodies positivity as well as baseline core set variables (SJC, TJC, PGA, EGA, ESR, CRP) and disease activity scores (DAS28-CRP, DAS28-ESR, SDAI and CDAI), as shown in Table IV. Patients in T2T period group were older (55 *vs*. 52 years, p=0.031) with shorter median disease duration (24 *vs*. 30 months, p=0.038) than patients in non-T2T group. There were more early stage RA patients (48% *vs*. 33%, p=0.003) and more treatment-naive patients (60% *vs*. 44%, p=0.001) in T2T period group in comparison with non-T2T period group (Table IV). In relation to initial therapy, the higher prescription rates of MTX (no significant difference) and HCQ (significant difference) and the proportional declining utilisation rate of LEF (no significant difference) were spotted (Table S1). Furthermore, the higher rate of drug combination treatment (87.5% *vs*. 71.4%, p<0.0001) was noticed in T2T group. On the other hand, the tighter control of patients after 2011 was measured by the significant higher average visit number per year at MDA/HDA (6.6 *vs*. 4.6, p<0.0001) and remission/LDA (3.6 *vs*. 2.8, p<0.0001) compared to the non-T2T period group in Table S1. Additionally, the higher rate of regular follow-up was also attained in the T2T group obviously (85% *vs*. 56%, p<0.0001). In a word, the aforementioned findings were partly supported the implementation of T2T in our department.

The cumulative percentage of remission

During 1 year follow-up, remission which was achieved at least once in patients treated with T2T strategy (T2T period group) was significantly higher than that in patients with usual care (non-T2T period group) (p<0.0001) as demonstrated by DAS28-CRP (73.2% *vs*. 47.2%, OR=2.4 (95% CI 1.7-3.2)), DAS28-ESR (61.5% *vs*. 34.5%, OR=2.4 (95% CI 1.7-3.5)), SDAI (52.4% *vs*. 21.3%, OR=3.0 (95% CI 1.9-4.8)), CDAI (49.3% *vs*. 19.1%, OR=2.8 (95% CI 1.8-4.5)). After adjusting OR for age, disease duration, early stage and treatment-naive rates by Cox proportional hazards regression model, patients treated with T2T strategy had about 2.5 times higher odds to reach remission during 1 year period (Fig. 4).

Time to achieve first remission

Within a 1-year period, time to first remission define by DAS28-CRP, DAS28-

Table II. Changes in disease activity before and after 2011.

	Disease activity scores		T /Z value	p-value
	Before T2T	After T2T		
mean DAS28-ESR	3.96 ± 1.55	2.93 ± 1.35	-6.16	<0.0001
mean DAS28-CRP	3.65 ± 1.43	2.62 ± 1.22	-6.45	<0.0001
mean SDAI	11.0 (4.2, 20.1)	5.2 (2.3, 11.4)	-10.27	<0.0001
mean CDAI	10.0 (4.0, 19.0)	5.0 (2.0, 10.0)	-12.20	<0.0001
AMDAS28-ESR	3.98 ± 1.48	2.80 ± 1.20	-5.39	<0.0001
AMDAS28-CRP	3.69 ± 1.38	2.51 ± 1.07	-5.81	<0.0001
AMSDAI	12.2 (6.1, 19.1)	5.4 (2.5, 10.8)	-9.04	<0.0001
AMCDAI	11.0 (5.5, 17.0)	5.0 (2.0, 9.8)	-8.58	<0.0001

Values are presented as mean (S.D.) or median (IQR), as applicable.
AM: adjusted-method; T/Z value: test statistics reported for Student's t-tests and Mann-Whitney U-tests, respectively.

Table III. Changes in remission rate before and after 2011.

	Remission rate %		OR (95% CI)	p-value
	Before T2T	After T2T		
mean DAS28-ESR	21.59	48.13	2.55 (2.08-3.11)	<0.0001
mean DAS28-CRP	25.61	58.59	2.78 (2.26-3.41)	<0.0001
mean SDAI	14.81	36.11	2.14 (1.69-2.71)	<0.0001
mean CDAI	18.18	34.28	2.14 (1.72-2.66)	<0.0001
AMDAS28-ESR	21.95	48.62	2.93 (2.07-4.14)	<0.0001
AMDAS28-CRP	31.91	61.21	3.55 (2.57-4.91)	<0.0001
AMSDAI	10.64	34.20	3.90 (2.45-6.18)	<0.0001
AMCDAI	12.77	33.74	3.06 (2.00-4.71)	<0.0001

Values are presented as mean (S.D.) or median (IQR), as applicable.
AM: adjusted-method; OR: odds ratio; CI: confidence interval.

Table IV. Baseline features of sub-cohort patients.

	non-T2T (n=119)	T2T (n=585)	p-value
Women, n (%)	97 (82%)	458 (78%)	0.443
Age, years	52 ± 15	55 ± 13	0.031
Disease duration, months media (IQR)	30 (10-120)	24 (6-88)	0.038
RF positive, n (%)	99/118 (84%)	443/578 (77%)	0.084
Anti-CCP positive, n (%)	99/112 (88%)	459/545 (84%)	0.261
Early stage, n (%)	38/116 (33%)	279/583 (48%)	0.003
Treatment-naïve, n (%)	51/117 (44%)	351/585 (60%)	0.001
SJC	3 (1-6)	2 (1-5)	0.143
TJC	6 (2-10)	4 (2-8)	0.129
ESR, mm/h	34 (19-50)	32 (18-50)	0.584
CRP, mg/l	9 (5-22)	10 (4-23)	0.615
PGA	52 ± 25	50 ± 23	0.556
EGA	47 ± 25	44 ± 21	0.180
DAS28-CRP	4.33 ± 1.21	4.16 ± 1.18	0.146
DAS28-ESR	4.77 ± 1.36	4.61 ± 1.25	0.215
SDAI	19.1 (13.2-32.0)	17.4 (11.3-26.9)	0.067
CDAI	18.0 (11.0-29.0)	16.0 (10.0-24.0)	0.051

Values are presented as mean (S.D.) or median (IQR), as applicable.
SD: standard deviation; IQR: interquartile ranges.

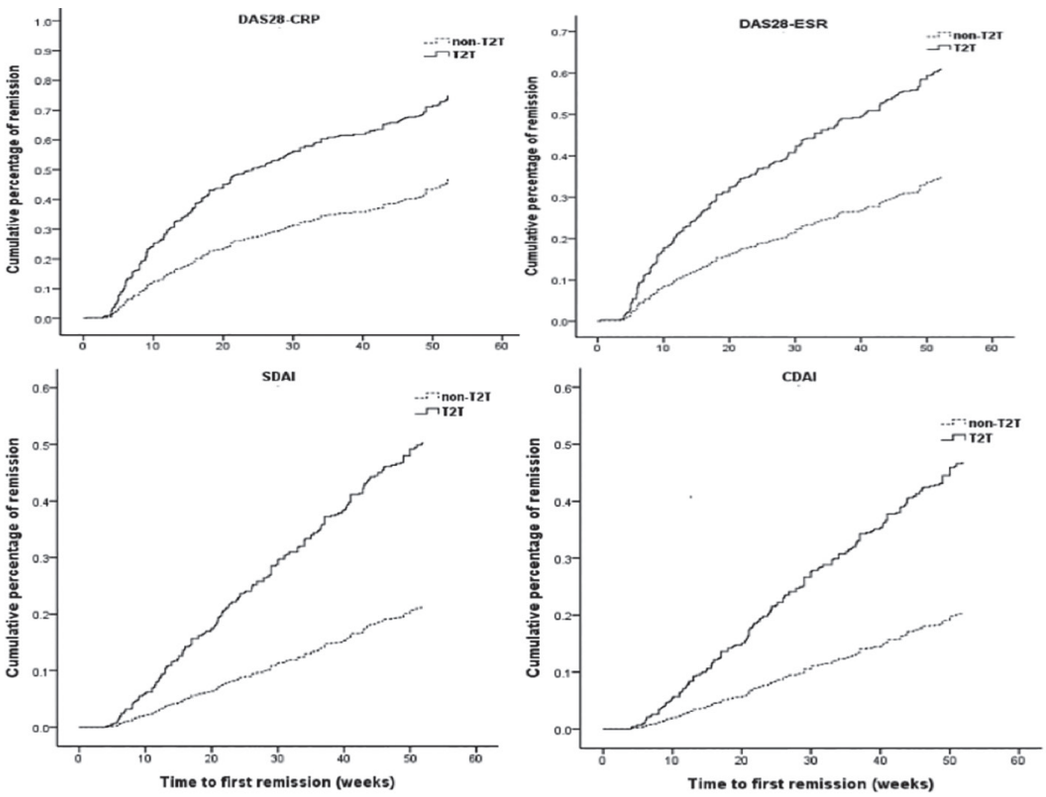

Fig. 4. Time to achieve first remission during 1 year of follow-up. Survival curve of time to reach remission for T2T and non-T2T periods groups within 1 year as demonstrated by DAS28-CRP, DAS28-ESR, SDAI and CDAI.

ESR was dramatically shorter in T2T group than in non-T2T group, with a median of 21 (95% CI: 17-25) and 37 (95% CI: 32-42) weeks *versus* a median over 52 weeks respectively ($p<0.0001$). Oppositely, SDAI, CDAI appeared to be stricter composite measures with prolonged median time to first remission (49 weeks, >52 weeks respectively) in T2T period group and with median over 52 weeks in routine care group (Fig. 4). Additionally, we also noticed that no obvious differences were seen between the patients fulfilled 1987 ACR classification criteria and fulfilled 2010 ACR/EULAR classification criteria in terms of cumulative percentage of remission and time to achieve first remission during the first-year follow-up (data not shown).

Table S1. T2T adherence during 1-year follow-up of sub-cohorts.

	non-T2T (n=119)	T2T (n=585)	*p*-value
Initial therapy			
MTX, n (%)	87 (73%)	472 (81%)	0.081
LEF, n (%)	74 (62%)	305 (52%)	0.055
HCQ, n (%)	30 (25%)	222 (38%)	0.009
SASP, n (%)	11 (9%)	22 (4%)	0.016
Glucocorticoids, n (%)	42 (35%)	239 (41%)	0.305
Biological agents, n (%)	10 (8%)	27 (5%)	0.112
DMARD combination, n (%)	85 (71%)	512 (88%)	<0.0001
Average number of visit per year during follow-up			
Patients in MDA/HDA	4.6 ± 2.7	6.6 ± 2.8	<0.0001
Patients in REM/LDA	2.8 ± 1.2	3.6 ± 1.4	<0.0001
Regular follow-up, n (%)	67 (56%)	496 (85%)	<0.0001

Values are presented as mean (S.D.) or median (IQR), as applicable.
REM: remission; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; SD: standard deviation; IQR: interquartile ranges.

Discussion

Reaching remission or alternatively LDA as early as possible has been the target in the management of RA in recent years. In current study, we investigated the secular trends in the disease activity as well as the status of reaching the target during 8 years, before and after the institution and adherence to T2T strategy, in real life clinical practice. Our data showed the overall trends in management of RA have made significant improvements, embodied in the gradual but steady decease in disease activity and increase in reaching remission or LDA annually during the nearly past decade. The changes seemed to be particularly dramatic between 2010 and 2011, which indicated that compliance with T2T approach in 2011 was strongly associated with greater decrease of disease activity and more rise in remission rate.

Disease activity and remission can be assessed by a variety of composite indices. Because the disparities between various validated indices have been confirmed in previous studies (26-28), we used multi-index to determine disease activity to ensure the reliability of our results. Very strikingly, similar trends were recorded with any of definitions employed in either mean or time-adjusted mean methods. The key value of T2T strategy was further supported by a sub-cohort study, showing significantly more patients in the T2T period group experienced remission at least once with shorter median time

to first remission compared to those in non-T2T period group.

In terms of the value of T2T, the results of this study were in accordance with those from published RCTs (5, 6) and cohort studies (7-10). A recent study in patients with early inflammatory arthritis, by comparing 1987-diven cohort (mild control) with 2010-driven cohort (intensive control), indicated the efficacy of more intensive treatment strategies in the management of early arthritis during 12-month follow-up (29). Precisely, in the current study, it was demonstrated that T2T strategy was more effective than the usual care even in suboptimal clinical setting, and compliance with the intervention not only achieve higher remission rates, but exerted a powerful effect on the goal of early remission. On the other hand, unlike to most of other researches where usually DAS28-ESR was applied to reflect disease activity condition, DAS28-CRP, SDAI, as well as CDAI were applied to evaluate the disease severity in present study. The overall trends were in line with each other, but the observed discrepancy indicated DAS28 are more achievable by contrast to SDAI, CDAI as regards reaching higher remission rates earlier. In addition, from our relative big data, there was a general agreement between DAS28-CRP and DAS28-ESR, while the mean value of DAS28-CRP was significantly smaller than that of mean DAS28-ESR approximately 0.3. This result was also consistent with other studies where one solution would be to derive a new set of cut-off points tailored for use with DAS28-CRP (28, 30). Interestingly, both of the annual remission rates in any kind of methods and the cumulative remission rates in the present study were dramatically higher than that of a previous nationwide cross-sectional study (only 6.8–8.6% with different criteria) carried out from July 2009 to January 2012 at 28 tertiary hospitals in China (11). The further plausible explanations for this apparent discrepancy in remission condition were warranted. To some extent, this nationwide study might fail to reflect the unbiased fact due to no specialised training and unitised treatment regimen. Conversely, the relative unified diagnostic and therapeutic patterns were set out in our centre, which were closely associated with the higher remission rates. Especially, under our national healthcare system where a patient is able to visit the clinic without appointment and sometimes visit several medical centres, three-year multi-centre investigation may hard to avoid double counting. On the other hand, it should be noted that, there was clear imbalance in levels of healthcare of 28 tertiary hospitals and levels of regional economy development. However, patients in our medical centre, one of the top hospitals in China, were provided with better healthcare. In this regard, the remission condition can be reasonably expected to be superior to the average of the country. On the top of that, one of the most important reasons accounting for the distinct discrepancy was the lower proportion of T2T-abiding management in the national cross-sectional study. Those enrolled participants in multi-centre study received insufficient treatment with only less than one third of patients received DMARDs treatment for more than 1 year and less than one-quarter of the patients were on GCs treatment, embodied in irregular visiting period, whereas 61.7% patients received the GCs in their initial treatment program in our study was in line with those reports from Western countries (31, 32). Lower prescription rates of conventional synthetic DMARDs in this national clinical study compared to the patients in our study (76.1% *vs*. 100%), especially MTX (53.3% *vs*. 79.6%) and HCQ (16.9% *vs*. 37.1%) and were also noticed. To sum up, the more aggressive strategies with tighter control and rational medications utilisation in our department were actively contributing to the higher probability of RA remission. Actually, to boost the patient compliance, our medical centre established a special outpatient clinic for RA patients a few years ago and hundreds of RA patients have been participating with appointment of regular intervals. Taken together, T2T-adherence therapy is expected to be key role in achieving satisfactory remission rate. More intriguingly, even though the prescription of biologics is rather low around 4% in our study, largely restricted by patient's economic status, health care system as well as potential risks of tuberculosis and hepatitis B in China, the remission rate was still pretty impressive in contrast to previous studies (5-10, 33). The consequence spoke volume about the pivotal part of conventional synthetic DMARDs in treatment protocol. But as an important part of T2T strategy especially for those refractory RA patients, biologics are helpful for disease activity control in more intensive protocol (34). Recently, some biologics have been added into the list of basic medical insurance in some provinces and it is supposed to further improve Chinese patients' outcome in the future.

The present study was the first to demonstrate the trend in disease activity measured by DAS28-CRP, DAS28-ESR, SDAI, and CDAI over nearly a decade. Specifically, the excellent progress achieved in this period was positively correlated with the widespread implementation of T2T strategy. Collectively, the study seems to provide the worldwide rheumatologists with more confidence about the efficacy of T2T strategy and the significance of conventional synthetic DMARDs in clinical routine.

There are some limitations in this study. First, bias is inevitable based on the nature of being a retrospective study. In order to minimise potential bias in the process of data collection, two rheumatologists were assigned and uncertain or discordance medical records were determined by the third one. Second, the exclusive written treatment protocol failed to be presented in this retrospective research due to various factors. However, for sure, the medication regimen in our medical centre was highly in compliance with the principles of the 2010 EULAR recommendations since 2011. Generally, we provides RA patients with complete evaluation, appropriate treatment adjustments and appointment for next clinic visit primarily based on the disease activity and ultrasonic manifestations. The higher number of visits and rate of regular follow-up since 2011 may be a microcosm of our T2T adherence in our department. Additionally, no radiographic and functional assessment over time was included in this study. Al-

though several studies had documented previously that patients who achieved remission, defined in any way, generally developed less radiological progression and less deterioration of physical function compared with patients who were not in remission (10, 34-37), we were not able to confirm the association in this study. The improvement in radiographic and functional assessment in our cohort needs to be described in future studies.

Conclusion

Our study, for the first time, showed that the management of RA has been steadily improved by decreasing disease activity and increasing remission rates throughout the past 8 years, and T2T strategy was directly attributable to the favourable improvement in real life clinical practice.

Acknowledgments

We would like to thank all the patients, rheumatology nurses and rheumatologists who contributed to our study.

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