Stricter treat-to-target in RA does not result in less radiographic progression: a longitudinal analysis in RA BIODAM

Ramiro, S.; Landewe, R.; Heijde, D. van der; Sepriano, A.; FitzGerald, O.; Ostergaard, M.; ... ; Maksymowych, W.P.

Rheumatology, 2023, **00**, 1–9
https://doi.org/10.1093/rheumatology/kead021
Advance access publication 16 January 2023
Original article

Clinical science

Stricter treat-to-target in RA does not result in less radiographic progression: a longitudinal analysis in RA BIODAM

Sofia Ramiro [1,2,*], Robert Landewé [2,3], Désirée van der Heijde [1], Alexandre Sepriano [1,4], Oliver FitzGerald [5], Mikkel Østergaard [6], Joanne Homik[7], Ori Elkayam [8], J. Carter Thorne [9], Maggie J. Larché [10], Gianfranco Ferraccioli [11], Marina Backhaus[12], Gilles Boire [13], Bernard Combe [14], Thierry Schaeverbeke[15], Alain Saraux [16], Maxime Dougados [17], Maurizio Rossini [18], Marcello Govoni [19], Luigi Sinigaglia [20], Alain G. Cantagrel [21], Cornelia F. Allaart [1], Cheryl Barnabe [22], Clifton O. Bingham III [23], Dirkjan van Schaardenburg [24], Hilde B. Hammer [25], Rana Dadashova [26], Edna Hutchings[26], Joel Paschke [26] and Walter P. Maksymowych [27]

[1]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[2]Department of Rheumatology, Zuyderland Medical Center, Heerlen, The Netherlands
[3]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, The Netherlands
[4]NOVA Medical School, Universidade Nova de Lisboa, Portugal
[5]Conway Institute for Biomolecular Research, School of Medicine, University College Dublin, Ireland
[6]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[7]Department of Medicine, University of Alberta, Edmonton, Canada
[8]Tel Aviv Sourasky Medical Center and the "Sackler" Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[9]The Arthritis Program Research Group, University of Toronto, Toronto, Canada
[10]Departments of Medicine and Pediatrics, Divisions of Rheumatology, Clinical Immunology and Allergy, McMaster University, Hamilton, Canada
[11]Catholic University of the Sacred Heart, Rome, Italy
[12]Park-Klinik Weissensee, Academic Hospital of the Charité, Berlin, Germany
[13]Department of Medicine/Division of Rheumatology, Centre Intégré Universitaire de Santé et de Services Sociaux de l'Estrie—Centre Hospitalier Universitaire de Sherbrooke (CIUSSS de l'Estrie-CHUS), University of Sherbrooke, Sherbrooke, Canada
[14]Department of Rheumatology, Montpellier University, Montpellier, France
[15]Department of Rheumatology, FHU ACRONIM, University Hospital of Bordeaux, University of Bordeaux, France
[16]LBAI, U1227, Université Brest, Inserm, CHU Brest, Brest, France
[17]Rheumatology Department, Paris Cité University, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France
[18]Rheumatology Unit, Department of Medicine, University of Verona, Verona, Italy
[19]Rheumatology Unit, S. Anna Hospital and University of Ferrara, Ferrara, Italy
[20]Department of Rheumatology, Gaetano Pini Institute, Milan, Italy
[21]Department of Rheumatology, CHU Toulouse, Paul Sabatier University, Toulouse, France
[22]Departments of Medicine and Community Health Sciences, University of Calgary, Alberta, Canada
[23]Johns Hopkins University, Baltimore, MD, USA
[24]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, The Netherlands
[25]Department of Rheumatology, Diakonhjemmet Hospital and Faculty of Medicine, University of Oslo, Oslo, Norway
[26]CARE Arthritis LTD, Alberta, Canada
[27]Department of Rheumatology, University of Alberta, Edmonton, Alberta, Canada

*Correspondence to: Sofia Ramiro, Department of Rheumatology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
E-mail: sofiaramiro@gmail.com

Abstract

Objectives: To investigate whether meticulously following a treat-to-target (T2T)-strategy in daily clinical practice will lead to less radiographic progression in patients with active RA who start (new) DMARD-therapy.

Methods: Patients with RA from 10 countries starting/changing conventional synthetic or biologic DMARDs because of active RA, and in whom treatment intensification according to the T2T principle was pursued, were assessed for disease activity every 3 months for 2 years (RA-BIODAM cohort). The primary outcome was the change in Sharp-van der Heijde (SvdH) score, assessed every 6 months. Per 3-month

Received: 25 October 2022. **Accepted:** 6 January 2023

interval DAS44-T2T could be followed zero, one or two times (in a total of two visits). The relation between T2T intensity and change in SvdH-score was modelled by generalized estimating equations.

Results: In total, 511 patients were included [mean (SD) age: 56 (13) years; 76% female]. Mean 2-year SvdH progression was 2.2 (4.1) units (median: 1 unit). A stricter application of T2T in a 3-month interval did not reduce progression in the same 6-month interval [parameter estimates (for yes *vs* no): +0.15 units (95% CI: −0.04, 0.33) for 2 *vs* 0 visits; and +0.08 units (−0.06; 0.22) for 1 *vs* 0 visits] nor did it reduce progression in the subsequent 6-month interval.

Conclusions: In this daily practice cohort, following T2T principles more meticulously did not result in less radiographic progression than a somewhat more lenient attitude towards T2T. One possible interpretation of these results is that the *intention* to apply T2T already suffices and that a more stringent approach does not further improve outcome.

Keywords: RA, treat-to-target, radiographic progression, outcomes

Rheumatology key messages

- More meticulously following T2T does not result in less radiographic progression than a more lenient attitude.
- Occasionally deviating from a more stringent approach will not lead to more structural damage.

Introduction

The management of RA has gone through a profound transformation in past decades. This change happened not only because of the broader availability of efficacious drugs, but also because of strategies leading to early diagnosis, prompt treatment with DMARDs and treat-to-target (T2T) strategies. According to current recommendations, treatment should be aimed at reaching a target of sustained remission or low disease activity [1]. This means following a T2T strategy, which requires monitoring disease activity regularly, aimed at a predefined treatment goal and intensifying treatment until the goal is reached [2].

T2T is known for its advantages and its effect on clinical outcomes [3, 4]. These have been shown in strategy trials and later also in cohort studies [5–10]. More recently, we have conducted a true longitudinal analysis in a cohort of unselected patients from daily clinical practice, the RA-BIODAM (BIOmarkers of joint DAMage) cohort. We have shown that following a T2T strategy, and particularly sustained T2T (i.e. following T2T in consecutive visits) in daily clinical practice leads to more patients meeting the most stringent remission criteria over time [10].

However, analysing the effect of T2T on disease activity outcomes includes some circularity, as T2T implies adjusting treatment according to a target, which is in turn based on disease activity. Hence, it is not surprising that following T2T indeed leads to better disease activity outcomes. When treating patients, we aim both to suppress inflammation and also to minimize progression of structural damage. The effect of T2T on the progression of structural damage has been previously analysed, but only in a few trials and with conflicting results [3, 4]. In the TICORA (Tight Control of RA) trial, the T2T arm showed significantly lower radiographic progression at 18 months compared with the usual care group [8], while in the CAMERA (Computer Assisted Management in Early RA) trial, no significant differences were seen [9]. Cohort studies have addressed the effect of T2T on clinical outcomes, but to our knowledge not on radiographic progression [5–7].

The impact of following a T2T strategy on radiographic progression is thus not yet clear. Moreover, a longitudinal analysis taking all observations over time into account, both in terms of following T2T or not, and radiographic progression has not yet been conducted and is helpful to shed light on this question. The aim of the present study was to investigate whether meticulously following a T2T strategy in patients with RA in daily clinical practice leads to lower radiographic progression.

Methods

Study population

Patients from RA-BIODAM (BIOmarkers of joint DAMage) were included [11]. RA-BIODAM is a 2-year multi-national prospective observational study, including patients with a clinical diagnosis of RA and also fulfilling the 2010 RA Classification Criteria [12], recruited in daily practice from 10 countries from October 2011 to April 2015. At inclusion in the cohort, patients had active disease (44-joint disease activity score, DAS44 > 2.4) [13] and were to be started on or to change DMARD treatment, including conventional synthetic DMARDs (csDMARDs) and a first TNF inhibitor (TNFi); patients who had prior biologic (b)DMARD experience were excluded. Patients were included in this analysis if they had at least one (6-, 12- or 24-month) interval with radiographic progression data available. The study fulfilled Good Clinical Practice Guidelines, received approval from the local ethics committees, and all patients provided written informed consent.

Individual ethics committees approving the project are listed in Supplementary Table S7, available at *Rheumatology* online.

Radiographic damage progression

Radiographic damage progression was the outcome of interest. Radiographic damage, assessed in radiographs of the hands and feet at 6-month intervals, was scored with the Sharp–van der Heijde method (SvdH) by two readers blinded for clinical data but aware of the chronological order [14, 15]. The average score of the readers was used. SvdH measures erosions and joint space narrowing in 44 different joints and provides an aggregated sum score ranging from 0 to 448. Radiographic progression was computed as change scores, e.g. 6-month progression reflects the difference between the status scores at 6 months and baseline, the latter subtracted from the former. Progression scores were calculated for each 6-month interval, for 12-month intervals and for the whole follow-up, i.e. 2-year interval.

Treat-to-target

Participating rheumatologists were required by protocol to follow a T2T strategy with DAS44 remission (DAS44 < 1.6) as benchmark. Following a DAS44-T2T remission strategy, which was defined at each 3-month visit, was the main variable of interest. T2T was considered as being followed: (i) if a patient had already a DAS below the target (DAS < 1.6) and treatment was not intensified; or (ii) if treatment was intensified upon a DAS ≥ 1.6. Treatment intensification was defined as increasing dosage or adding a drug from the following categories: csDMARDs, bDMARDs, targeted synthetic DMARDs (tsDMARDs) or glucocorticoids. T2T was considered incorrectly applied if: (i) the target was met, but treatment was nevertheless intensified; or (ii) the target was not met, but treatment was not intensified.

For each patient and throughout 21 months of follow-up, the proportion of visits out of the total number of visits of that patient (maximum eight) in which T2T was followed was calculated. This proportion was split into quartiles to categorize patients based on the proportion of visits in which T2T was followed according to our definition: very low, ≤40% of the visits; low, >40% and <62.5%; high, ≥62.5% and ≤75%; and very high, >75%. The 2-year visit was left out on purpose so that the analysis could reflect a time lag between following T2T (up to 21 months) and the 2-year radiographic progression as the outcome.

Per 3-month interval, T2T could be followed zero, one or two times (total of two visits, one at the start and one at the end) (Fig. 1). To investigate the relationship between following T2T and radiographic progression, which could be computed in different intervals, the number of visits following T2T in each 3-month period was used. For the main analysis, the effect of following T2T in each 3 months was used and following T2T two times (or one time) was compared with not following it (i.e. 0 times) (Fig. 1). When different intervals were considered for following T2T (see below), a different total number of visits following T2T was possible, always considering that visits took place every 3 months (Supplementary Fig. S1, available at *Rheumatology* online).

Additional definitions for T2T were also considered for sensitivity analyses: (i) T2T without glucocorticoids, i.e. without considering glucocorticoids as a treatment intensification; (ii) T2T less strict, i.e. considering T2T as adequate as long as the target, DAS44 remission, is met, regardless of whether treatment is nevertheless intensified or not; (iii) T2T-low disease activity (T2T-LDA) using LDA (i.e. DAS < 2.4) [16] instead of remission as the benchmark.

Statistical analysis

Descriptive analysis was conducted, and the characteristics of patients grouped according to quartiles of 2-year radiographic progression or quartiles of proportion of visits following T2T were compared using ANOVA for continuous variables and χ^2 for categorical variables. Radiographic progression at 2 years was visualized across groups by cumulative probability plots.

The relationship between the number of visits following T2T in each 3-month interval and 6-month radiographic progression in the same interval was investigated using generalized estimating equations (GEE) (Fig. 1A). Additionally, the association between the number of visits following T2T in each 3-month interval and 6-month radiographic progression in the subsequent 6-month interval was investigated, allowing a lag of at least 3 months between the main predictor of interest (i.e. following T2T) and the outcome (i.e. radiographic progression) to ensure that the outcome was occurring later than the predictor (Fig. 1B). GEE is a suitable technique for longitudinal analysis, which makes use of all available observations from each patient while adjusting for inherent within-subject correlations of the repeated measurements. The 'exchangeable' working correlation structure was used.

To address the possibility that a larger time lag is required to see an effect of following T2T on radiographic progression, additional analyses were conducted (schematic representations of the analysis: Supplementary Figs S1–S3, available at *Rheumatology* online). The first analysis used 2-year radiographic progression as the outcome. The effect of the number of visits following T2T (compared with not following) was tested, considering different intervals (in different models): first

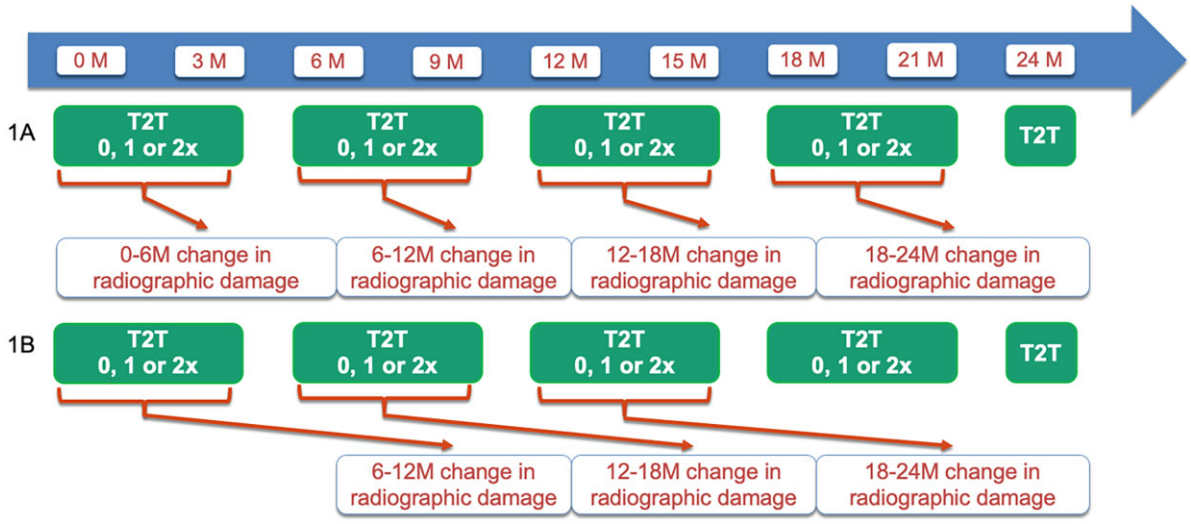

Figure 1. Schematic representation of the statistical analysis. Associations between the number of visits with T2T in a 3-month interval and 6-month change in radiographic damage, both in the same (**A**) and in the subsequent 6-month interval (**B**) over a total period of 2 years (**A** and **B** depict separate models). T2T: treat-to-target

3 months (2 visits), 6 months (3 visits), 9 months (4 visits) and 12 months (5 visits) (Supplementary Fig. S1, available at *Rheumatology* online). The same analysis using different intervals and corresponding number of visits following T2T was conducted with 12-month radiographic progression, taking place between 12 months and 2 years, as the outcome, allowing for a lag between following T2T and radiographic progression (Supplementary Fig. S2, available at *Rheumatology* online). Lastly, the effect of following T2T was also computed as the groups defined based on the proportion of visits following T2T (very low, low, high and very high as described above), and their effect was analysed on the 2-year radiographic progression (Supplementary Fig. S3, available at *Rheumatology* online).

For each model, interactions between the T2T variable and age, gender, disease duration and RF/ACPA-positivity were tested, and, if significant ($P < 0.15$) and clinically relevant, the model was fitted in each subgroup. If these proved to be not relevant, final models were adjusted for potential confounders selected *a priori*: age, gender, disease duration and country of residence. In addition, RF/ACPA positivity was tested as possible confounder and included in the models if its addition changed the effect of the main variable of interest importantly. Stata SE version 16 was used.

Results

In total, 521 patients were included (91% of the RA-BIODAM cohort) with a mean age of 56 (S.D. 13) years, 76% females and a mean disease duration of 6.5 (7.8) years (Supplementary Table S1, available at *Rheumatology* online). Seventy-eight per cent of the patients were RF and/or ACPA positive, and 48% were DMARD-naive at baseline. The mean SvdH score at baseline was 17.0 (28.8) and at 2 years it was 20.3 (33.0) ($n = 482$ and $n = 363$, respectively) (Supplementary Table S2, available at *Rheumatology* online). Taking all 6-month intervals during follow-up, the average 6-month progression was 0.6 (1.4). At 2 years, patients showed on average 2.2 (4.1) units progression (median: 1 unit; $n = 413$).

When comparing patients grouped according to the quartiles of 2-year radiographic progression, patients with higher progression were older, had longer disease duration, more comorbidities and higher baseline radiographic damage (Table 1). There were no differences in the remaining baseline demographic and clinical characteristics. Moreover, there were no differences in treatment over follow-up, namely in the proportion of patients on TNFi, non-TNFi bDMARDs or tsDMARDs (Table 1). During follow-up, patients with the highest radiographic progression had the highest DAS44, but there was no clear dose relationship across groups.

Over 21 months of follow-up, T2T was followed, on average, in 4.4 (1.9) visits (median: 4), corresponding to 59% (S.D. 24%) of all visits available (Supplementary Table S3, available at *Rheumatology* online). In <1% of the patients, T2T was never followed, and in 9% of the patients T2T was followed in all available visits. Across quartiles of the proportion of visits with T2T followed, patients with higher proportion of visits followed were younger, less frequently females, had fewer comorbidities, and lower baseline DAS44 and HAQ (Supplementary Table S4, available at *Rheumatology* online). There were no differences in treatment over follow-up across the quartiles of proportion of visits following T2T. Over follow-up the DAS44 was significantly lower in the group following most T2T, with an inverse dose relationship between the proportion of visits following T2T and mean DAS44 [DAS44 4.1 (0.9) in the very low and 3.6 (1.0) in the very high group].

T2T and radiographic progression

During the 2 years of follow-up, radiographic progression was not significantly different across categories of T2T followed: very low with 2.1 (2.7) units; low, 2.8 (6.0); high, 2.4 (4.5); and very high, 1.6 (2.2) units (Fig. 2).

Taking the whole follow-up into account, following T2T in a 3-month interval was not associated with radiographic progression in the same 6-month interval [parameter estimates (for yes *vs* no)]: +0.15 units (95% CI: −0.04, 0.33) for 2 *vs* 0 visits following T2T; and +0.08 units (−0.06 to 0.22) for 1 *vs* 0 visits following T2T (Table 2). Similarly, following T2T in a 3-month interval was not associated with radiographic progression in the subsequent 6-month interval (Table 3). Sensitivity analyses, with different definitions of T2T, retrieved similar results (Tables 2 and 3).

The effect of following T2T a certain number of times *vs* not following it within an initial period of follow-up (first 3 months and subsequently also 6 months, 9 months and 12 months) on radiographic progression over 2 years was not statistically significant. The categories according to the proportion of visits in which T2T was followed were not associated with 2-year radiographic progression (Supplementary Table S5, available at *Rheumatology* online; Fig. 2).

Considering a possible delay between following T2T and its effect on radiographic progression, the effect of following T2T in the first 3 months (6, 9 and 12 months) was analysed on radiographic progression, again showing no significant relationship (Supplementary Table S6, available at *Rheumatology* online).

Discussion

In this daily practice cohort, we have shown that pursuing a stricter form of T2T did not result in less radiographic progression than using a more lenient form. With T2T principles being followed in 60% of the visits and almost all patients having visits with and without T2T followed throughout the 2-year follow-up, this result suggests that a somewhat more lenient attitude towards T2T will not lead to worse structural outcomes compared with following T2T principles more meticulously.

Disease activity is one of the well-known factors that predispose to radiographic progression [17–19]. If a T2T-strategy is recommended to keep the disease activity controlled and namely achieve more remission, and if following T2T leads to more patients meeting the most stringent remission criteria over time [10], why then does following T2T better not appear to prevent radiographic progression?

One possible interpretation of these results is that the *intention* to apply T2T already suffices, and that a more stringent approach does not further improve outcome. T2T was applied in 60% of the visits, in almost all patients in at least one visit (99%), while only a minority followed T2T in all visits (9%). This confirms that there was the general intention to follow the protocol and apply T2T, but this was not thoroughly followed in every single visit. It is therefore possible that the important benefit of preventing radiographic damage

Table 1. Demographic and clinical characteristics (at baseline and over follow-up) of patients stratified by the proportion of 2-year radiographic progression

	Radiographic progression over 24 months ($n = 413$)[a]			
	Very low (≤0.5) $n = 164$	Low (>0.5 & ≤1) $n = 52$	High (>1 & <3) $n = 104$	Very high (≥3) $n = 93$
Baseline characteristics				
Age, years	**52 (12)**	**57 (11)**	**57 (13)**	**59 (12)**
Female gender	131 (80%)	43 (83%)	77 (74%)	67 (73%)
Disease duration, years	**5 (7)**	**8 (8)**	**7 (8)**	**8 (9)**
Education, years	13 (4)	12 (4)	13 (4)	13 (4)
Number of comorbidities	**0.9 (1.1)**	**1.0 (1.1)**	**1.3 (1.3)**	**1.2 (1.3)**
RF positivity	101 (64%)	30 (63%)	75 (74%)	65 (73%)
ACPA positivity	107 (67%)	33 (64%)	73 (70%)	68 (74%)
RF and/or ACPA positivity	118 (74%)	36 (71%)	81 (79%)	79 (87%)
Sharp–van der Heijde score (0–448)	**8.7 (17.6)**	**18.4 (30.6)**	**18.2 (30.0)**	**30.3 (42.3)**
DAS44 (0-10)	3.8 (1.0)	3.9 (1.0)	3.8 (1.0)	3.9 (1.0)
Patient Global Assessment (0–10)	5.5 (2.2)	6.3 (2.1)	5.7 (2.6)	5.7 (2.2)
Physician Global assessment (0–10)	5.4 (1.8)	6.0 (1.8)	5.6 (1.9)	5.8 (2.0)
SJC (0–44)	8.1 (6.1)	8.7 (6.0)	8.3 (5.6)	9.0 (5.9)
TJC (0–53)	13.7 (9.1)	13.6 (8.3)	12.7 (9.2)	14.1 (8.5)
HAQ (0–3)	1.1 (0.6)	1.2 (0.6)	1.1 (0.6)	1.1 (0.7)
ESR (mm/h)	26.3 (20.0)	27.1 (20.6)	28.2 (21.3)	30.1 (21.5)
CRP (mg/L)	12.4 (17.9)	13.4 (15.7)	14.8 (20.5)	17.7 (28.2)
Number of previous csDMARDs	0.8 (1.1)	1.1 (1.3)	0.8 (1.0)	1.0 (1.3)
DMARD naive	82 (50%)	22 (42%)	57 (55%)	44 (48%)
Smoking status				
Never smoker	80 (49%)	22 (42%)	51 (49%)	50 (54%)
Current smoker	47 (29%)	12 (23%)	26 (25%)	24 (26%)
Ex-smoker	36 (22%)	18 (35%)	27 (26%)	18 (20%)
Academic center	111 (68%)	33 (64%)	75 (72%)	58 (63%)
Clinical characteristics over 21 months				
Proportion of visits with T2T followed (0–1)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
TNFi ever	88 (54%)	27 (52%)	53 (51%)	56 (60%)
Non-TNFi bDMARD ever	12 (7%)	11 (21%)	7 (7%)	17 (18%)
tsDMARD ever	1 (1%)	0 (0%)	1 (1%)	2 (2%)
csDMARD only	75 (46%)	21 (40%)	51 (49%)	32 (35%)
TNFi 1st year only	13 (15%)	6 (22%)	4 (8%)	10 (18%)
Non-TNFi bDMARD 1st year only	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of visits on TNFi (0–8)	3.3 (3.6)	2.6 (3.2)	3.3 (3.6)	3.6 (3.4)
Number of visits on non-TNFi bDMARD (0–8)	0.4 (1.5)	1.1 (2.4)	0.3 (1.2)	0.7 (1.8)
Number of csDMARDs (0–6)	1.8 (1.0)	2.2 (1.2)	1.8 (1.0)	1.9 (1.0)
Number of bDMARDs (0–5)	0.4 (0.5)	0.4 (0.5)	0.4 (0.5)	0.4 (0.5)
DAS44 (0–10)	**2.2 (0.9)**	**2.3 (0.8)**	**2.1 (0.7)**	**2.5 (0.8)**

In bold are the characteristics with a statistically significant difference across the groups highlighted.
[a] Total of patients with 24-month radiographic progression interval available. Categories defined based on quartiles of 24-month radiographic progression. bDMARD: biological DMARD; csDMARDs: conventional synthetic DMARDs;DAS44: 44-joint DAS; DAS28-ESR: 28-joint score DAS with ESR; SJC: swollen joint count; T2T: treat-to-target; TJC: tender joint count; TNFi: TNF inhibitor; tsDMARD: targeted synthetic DMARD.

progression was obtained by this overall intention to apply T2T. On top of that, meticulously following T2T, i.e. following it more often or always compared with not following it (in some visits), does not seem to provide additional benefit in terms of structural damage. Alternatively, it is possible though that an earlier start of appropriate treatment, namely before structural damage starts to develop, is more of value than a stricter application of T2T once some damage has accrued. This can explain these negative results in a population with a mean of 7 years of disease duration. Although we did not find an interaction with disease duration, we cannot exclude that the results could be different if the analysis was restricted to an early RA, DMARD-naive, population. This can also explain the discrepancy between our results and the ones from TICORA, the only RCT in which T2T has been shown to inhibit radiographic progression, as in TICORA only patients with up to 5 years of disease were included [8]. Another possible explanation for T2T not inhibiting radiographic progression may lie on limitations of the disease activity assessment. A DAS44 score may be elevated mainly due to a higher tender joint count or patient's global assessment of disease activity in the absence of more objective signs of inflammation, leading the clinician to decide to not intensify treatment. Such a situation, formally not following T2T, may not lead to more radiographic progression as swollen joint count and acute phase reactants have the strongest associations with damage progression [20–22]. Furthermore, treatment with bDMARDs is also known to uncouple the classic relationship between disease activity and radiographic progression, which could in turn also contribute to explain this lack of effect of T2T, as more than half of the patients in RA-BIODAM were at some point treated with bDMARDs [23, 24].

While T2T is advantageous and leads to positive outcomes at the group level, evidence is accumulating that it may not be the optimal approach at the individual patient level if

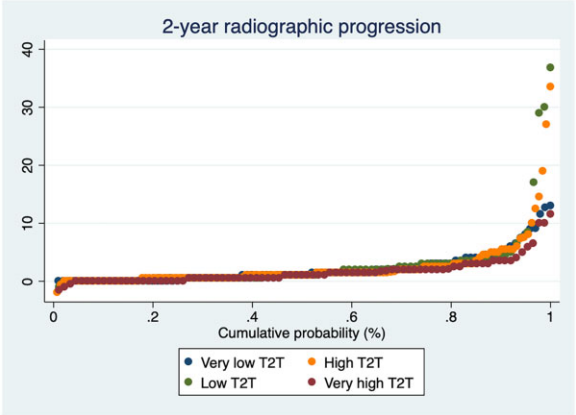

Figure 2. Cumulative probability plot with 2-year radiographic progression according to the proportion of 3-monthly visits with T2T followed. The proportion of visits in which T2T was followed was split into quartiles so that patients could be categorized based on the proportion of visits in which T2T was followed according to our definition: very low, ≤40% of the visits; low, >40% and <62.5%; high, ≥62.5% and ≤75%; and very high, >75%

followed too strictly, especially if not taking other factors that can influence disease activity score into account [25–28]. In general, T2T principles are correct, and one should aim at a remission or low disease activity state. However, the evidence of the virtues of T2T is mainly related to bringing patients with a high level of disease activity into a lower inflammatory state. When disease activity is already low or moderate, there is no evidence as to whether it is further beneficial to target remission. Actually, for patients in a low disease activity, further treatment intensification aimed at disease activity remission has not been shown to result in meaningful functional improvement [26]. Our study adds to this by underlining that, beyond an overall and global use of T2T, there is not really a need to meticulously follow T2T as it will not translate into better structural outcomes. Overtreatment is a potential problem that can precisely arise from being too strict in applying T2T, which should be considered in light of the current findings [25]. These data notwithstanding, the importance of measuring disease activity should still be emphasized, and the results of our study should be interpreted in the context of being regularly informed about the patient's disease activity and

Table 2. Effect of following DAS44-T2T-remission strategy on 6-month radiographic progression, measured in the same 6-month period as T2T, over 2 years[a]

	Change in radiographic damage [regression coefficient (95% CI)] $n = 506$	
	2 times vs 0 followed	1 time vs 0 followed
Main analysis T2T remission		
T2T during 3 months on radiographic progression in the same 6-month period	0.15 (−0.04, 0.33)	0.08 (−0.06, 0.22)
Sensitivity analysis		
T2T without glucocorticoids		
T2T during 3 months on radiographic progression in the same 6-month period	0.13 (−0.06, 0.31)	0.11 (−0.03, 0.25)
T2T less strict		
T2T during 3 months on radiographic progression in the same 6-month period	0.13 (−0.06, 0.32)	0.10 (−0.04, 0.25)
T2T low disease activity		
T2T during 3 months on radiographic progression in the same 6-month period	0.11 (−0.03, 0.24)	0.12 (−0.00, 0.25)

[a] All models (per row a separate model) adjusted for age, gender, disease duration and country. Analysis conducted as outlined in the schematic representation of Fig. 2A. T2T was considered being followed: (i) if a patient had already a disease activity score below the target (DAS < 1.6; DAS < 2.4 for LDA definition) and treatment was correctly not intensified; or (ii) if treatment was intensified upon a DAS ≥ 1.6 (or DAS ≥2.4 for LDA definition). T2T without glucocorticoids: without considering glucocorticoids in treatment intensification. T2T less strict: considering T2T as adequate as long as the target, DAS44 remission, is met, regardless of whether treatment nevertheless intensified or not.
DAS44: 44-joint disease activity score; T2T: treat-to-target.

Table 3. Effect of following DAS44-T2T-remission strategy on 6-month radiographic progression, measured in the subsequent 6-month period, compared with T2T, over 2 years[a]

	Change in radiographic damage [regression coefficient (95% CI)] $n = 506$	
	2 times *vs* 0 followed	1 time *vs* 0 followed
Main analysis T2T remission		
T2T during 3 months on radiographic progression in the subsequent 6-month period	−0.09 (−0.28, 0.10)	−0.10 (−0.24, 0.05)
Sensitivity analysis		
T2T without glucocorticoids		
T2T during 3 months on radiographic progression in the subsequent 6-month period	−0.10 (−0.28, 0.07)	−0.05 (−0.20, 0.10)
T2T less strict		
T2T during 3 months on radiographic progression in the subsequent 6-month period	−0.08 (−0.28, 0.11)	−0.10 (−0.25, 0.06)
T2T low disease activity		
T2T during 3 months on radiographic progression in the subsequent 6-month period	−0.03 (−0.20, 0.14)	0.06 (−0.12, 0.24)

[a] All models (per row a separate model) adjusted for age, gender, disease duration and country. Analysis conducted as outlined in the schematic representation of Fig. 2B. T2T was considered being followed: (i) if a patient had already a disease activity score below the target (DAS < 1.6; DAS < 2.4 for LDA definition) and treatment was correctly not intensified; or (ii) if treatment was intensified upon a DAS ≥ 1.6 (or DAS ≥2.4 for LDA definition). T2T without glucocorticoids: without considering glucocorticoids in treatment intensification. T2T less strict: considering T2T as adequate as long as the target, DAS44 remission, is met, regardless of whether treatment nevertheless intensified or not. DAS44: 44-joint disease activity score; T2T: treat-to-target.

having a general intention to implement T2T. These results should by no means be interpreted as indicating that frequent assessment of disease activity and T2T do not matter and should not be implemented.

Some limitations of this study need to be considered. First, it is possible that a longer follow-up, particularly after the application of T2T, would be necessary to capture an effect of T2T on radiographic progression as nowadays patients have lower levels of radiographic progression, which results in a limited power to identify factors significantly associated. Confounding by indication is also a potential concern in this analysis. Patients were not randomly allocated to T2T *vs* no T2T. In the same cohort we have previously reported that T2T was more followed in ACPA-positive patients and patients with more swollen joints and these are patients at a higher risk of radiographic progression, which in turn may have an impact on the current results [29]. Nevertheless, even though some statistical methods like propensity scoring could be used to partially address bias introduced by confounding by indication, the results of all analyses of our study, with different definitions of T2T or of radiographic progression, were consistent and provided the same conclusion. It is thus unlikely that confounding by indication fully explains the lack of effect of T2T on radiographic progression. Moreover, to fully overcome confounding by indication, an RCT would in theory be necessary, but given the known benefits of T2T it would not be ethical to randomize a patient to 'never T2T' (*vs* 'always T2T'), particularly for a long period [23]. Additionally, RCT would provide prognostic similarity at baseline, but as T2T is an iterative and adaptative process throughout follow-up, several reasons other than the treatment allocation could influence the decision to follow it or not. Although the effect that we were interested in analysing was that of T2T on radiographic progression, it is challenging or technically almost impossible to separate this effect from the effect of the individual treatment options used in the T2T approach as these options and the order in which at least some drug classes are used are inherent to applying T2T. Treatment with bDMARDs in general is associated with less radiographic progression than treatment with csDMARDs and also known to uncouple the relationship between disease activity and radiographic progression [23, 24, 30, 31].

The study also has several strengths, the most important being its multinational observational study design, which means that it includes unselected patients and interventions that can vary over time (following T2T *vs* not) reflecting daily clinical practice, with a true longitudinal analysis addressing the impact of following a T2T strategy on radiographic progression.

In this daily practice cohort, more meticulously following T2T principles did not result in more reduction of radiographic progression than a somewhat more lenient attitude towards T2T. While the T2T principles themselves are not disputed here, this study gives room to allow occasional deviations from a more stringent approach without major consequences, for instance when the rheumatologist considers further immunosuppressive treatment intensification not entirely appropriate.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article.

Contribution statement

S.R. drafted the first version of the manuscript. All authors made contributions to conception and/or implementation of the study, were involved in reviewing and revising the manuscript, and gave final approval to the version to be published.

Funding

BIODAM was financially supported by an unrestricted grant from AbbVie. The funder had no role in the design, performance, analysis, interpretation or reporting of the study, in the writing of the report or in the decision to submit the paper for publication.

Disclosure statement: S.R.: research grants and/or consultancy fees: AbbVie, Eli Lilly, Galapagos MSD, Novartis, Pfizer, UCB, Sanofi. R.L.: received consulting fees from AbbVie, BMS, Celgene, Eli-Lilly, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Roche, UCB and is Director of Rheumatology Consultancy bv. D.vdH.: received consulting fees from AbbVie, Bayer, BMS, Cyxone, Eisai, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Lilly, Novartis, Pfizer, UCB Pharma and is Director of Imaging Rheumatology bv. A.S.: received speaking fees from Novartis. O.F.:has received research grants and/or consultancy fees: AbbVie, Novartis, UCB, Pfizer, Janssen. M.Ø.: has received research grants from Abbvie, BMS, Merck and Novartis and speaker and/or consultancy fees from Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Gilead, Janssen, MEDAC, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB. J.H.: none. O.E.: has received grants and personal fees from Pfizer, Abbvie, Roche, Janssen, Novartis and Lilly; J.C.T.: received research grants and/or consulting fees from AbbVie, Pfizer, Sandoz; M.J.L.: received advisory board honoraria from AbbVie, Actelion, Boehringer Ingelheim, BMS, Fresenius-Kabi, Gilead, Janssen, Novartis, Pfizer, Sanofi, Roche; and an unrestricted educational grant from AbbVie. G.F.: received research grants and/or consultancy fees from Novartis, Roche, BMS, Pfizer, AbbVie, Lilly, Janssen, MSD, Boehringer-Ingelheim, UCB. M.B.: received research grants from: AbbVie Co.KG, Roche, Novartis, Pfizer and speaking fees from: AbbVie Co.KG, Amgen, BMS; Galapagos, Janssen, Lilly, MSD, Novartis, Sanofi Genzyme, Roche, Pfizer, UCB. G.B.: received consulting fees from Eli Lilly, Janssen, Novartis, Pfizer, Samsung BioEpis, Viatris and speaker fees from BMS, Merck, Pfizer, Viatris and industry support for investigator-initiated research initiatives from Abbvie, Amgen, BMS, Eli Lilly, Janssen, Merck, Pfizer. B.C.: received consulting fees and or research grants from AbbVie, Celltrion, Eli-Lilly, Fresenius, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Roche-Chugai. T.S.: received consulting fees for Lilly, Novartis, Pfizer, Sanofi and research financial support from: Pfizer, Lilly. A.S.: research grants and/

or consultancy fees from AbbVie, BMS, Roche Chugai, Eli Lilly, Nordic, Novartis, Sanofi, UCB, Galapagos. M.D.: received research grants and/or honorarium fees for his participation at advisory boards and/or symposium organized by Pfizer, AbbVie, Lilly, Novartis, BMS, Roche, UCB, Merck. M.R.: has received advisory board honoraria, consultancy fees and/or speaker fees from Amgen, Abbvie, BMS, Eli-Lilly, MSD, Novartis, Pfizer, UCB, Menarini, Theramex, Galapagos. M.G.: has received advisory board honoraria from Abbvie, BMS, Eli-Lilly, Galapagos, Pfizer and consultancy fees and/or speaker fees from Abbvie, Alfa-Sigma, BMS, Celgene, MSD, Novartis, Pfizer, Roche, Sanofi. L.S.: none. A.G.C.: received consultancy fees from BMS, Chugai, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, AbbVie, Celgene, Nordic Pharma and received research grants from Pfizer, UCB, AbbVie, Celgene. C.F.A: none. C.B.: advisory board honoraria from Gilead, Sanofi Genzyme and Celltrion Healthcare and speaking fees from Sanofi Genzyme, Pfizer, Janssen and Fresenius Kabi. C.O.B.: consultant to Abbvie, BMS, Janssen, Lilly, Pfizer, Sanofi and grant support from BMS. D.vS.: none. H.B.H.: has received fees for speaking and/or consulting from AbbVie, BMS, Pfizer, UCB, Novartis, Eli-Lilly. R.D.: none. E.H.: none. J.P.: none. W.P.M.: received consulting fees from AbbVie, Boehringer Ingelheim, Celgene, Eli-Lilly, Galapagos, Janssen, Novartis, Pfizer, UCB Pharma and is Chief Medical Officer of CARE Arthritis Limited.

Acknowledgements

The authors sincerely thank the staff and all patients of the RA BIODAM study.

References

1. Smolen JS, Landewe RBM, Bijlsma JWJ *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–99.
2. Smolen JS, Breedveld FC, Burmester GR *et al.* Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.
3. Schoels M, Knevel R, Aletaha D *et al.* Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis 2010;69:638–43.
4. Schipper LG, van Hulst LT, Grol R *et al.* Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology 2010;49:2154–64.
5. Vermeer M, Kuper HH, Hoekstra M *et al.* Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Arthritis Rheum 2011;63:2865–72.
6. Schipper LG, Vermeer M, Kuper HH *et al.* A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. Ann Rheum Dis 2012;71:845–50.
7. Brinkmann GH, Norvang V, Norli ES *et al.* Treat to target strategy in early rheumatoid arthritis versus routine care – a comparative clinical practice study. Semin Arthritis Rheum 2019;48:808–14.
8. Grigor C, Capell H, Stirling A *et al.* Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263–9.
9. Verstappen SM, Jacobs JW, van der Veen MJ *et al.* Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007;66:1443–9.
10. Ramiro S, Landewe RB, van der Heijde D *et al.* Is treat-to-target really working in rheumatoid arthritis? a longitudinal analysis of a cohort of patients treated in daily practice (RA BIODAM). Ann Rheum Dis 2020;79:453–9.
11. Maksymowych WP, FitzGerald O, Ostergaard M *et al.* Outcomes and findings of the international rheumatoid arthritis (RA) BIODAM cohort for validation of soluble biomarkers in RA. J Rheumatol 2020;47:796–808.
12. Aletaha D, Neogi T, Silman AJ *et al.* 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.
13. van der Heijde DM, van 't Hof MA, van Riel PL *et al.* Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916–20.
14. van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, vad de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;8646:1036–8.
15. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261–3.
16. van Gestel AM, Prevoo ML, van 't Hof MA *et al.* Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34–40.
17. Welsing PM, Landewe RB, van Riel PL *et al.* The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50:2082–93.
18. Aletaha D, Funovits J, Breedveld FC *et al.* Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. Arthritis Rheum 2009;60:1242–9.
19. Ten Klooster PM, Versteeg LGA, Oude Voshaar MAH *et al.* Radiographic progression can still occur in individual patients with low or moderate disease activity in the current treat-to-target paradigm: real-world data from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Arthritis Res Ther 2019;21:237.
20. van der Heijde DM, van Riel PL, van Leeuwen MA *et al.* Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. Br J Rheumatol 1992;31:519–25.
21. Klarenbeek NB, Guler-Yuksel M, van der Heijde DM *et al.* Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. Ann Rheum Dis 2010;69:2107–13.
22. Cheung PP, Mari K, Devauchelle-Pensec V *et al.* Predictive value of tender joints compared to synovitis for structural damage in rheumatoid arthritis. RMD Open 2016;2:e000205.
23. Smolen JS, Han C, van der Heijde DM *et al.* Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 2009;68:823–7.
24. Landewe R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis Rheum 2006;54:3119–25.
25. Landewe RBM. Overdiagnosis and overtreatment in rheumatology: a little caution is in order. Ann Rheum Dis 2018;77:1394–6.
26. Bergstra SA, Olivas O, Akdemir G *et al.* Further treatment intensification in undifferentiated and rheumatoid arthritis patients already

in low disease activity has limited benefit towards physical functioning. Arthritis Res Ther 2017;19:220.
27. Ferreira RJO, Carvalho PD, Ndosi M *et al.* Impact of patient's global assessment on achieving remission in patients with rheumatoid arthritis: a multinational study using the METEOR database. Arthritis Care Res 2019;71:1317–25.
28. Ferreira RJO, Ndosi M, de Wit M *et al.* Dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis. Ann Rheum Dis 2019;78:e109.
29. Sepriano A, Ramiro S, FitzGerald O *et al.* Adherence to treat-to-target management in rheumatoid arthritis and associated factors: data from the International RA BIODAM cohort. J Rheumatol 2020;47:809–19.
30. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF *et al.* Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381–90.
31. Platzer A, Alasti F, Smolen JS *et al.* Trajectory clusters of radiographic progression in patients with rheumatoid arthritis: associations with clinical variables. Ann Rheum Dis 2022;81:175–83.