Adherence to Treat-to-Target Management in Rheumatoid Arthritis and Associated Factors: Data from the International RA BIODAM Cohort

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Short running title: Treat-to-Target Rheumatoid Arthritis

ABSTRACT

Background. Compelling evidence supports a treat-to-target (T2T) strategy for optimal outcomes in rheumatoid arthritis (RA). There is limited knowledge regarding the factors that impede implementation of T2T, particularly in a setting where adherence to T2T is protocol specified. We aimed to assess clinical factors that associate with failure to adhere to T2T.

Methods. RA patients from 10 countries starting or changing conventional synthetic disease-modifying anti-rheumatic (csDMARDs) drugs and/or starting tumor necrosis factor inhibitor (TNFi) were followed for 2 years (RA BIODAM cohort). Participating physicians were required per-protocol to adhere to the T2T strategy. Factors influencing adherence to T2T low disease activity (T2T-LDA; DAS≤2.4) were analyzed in two types of binomial generalized estimating equations (GEE) models: i. including only baseline features (baseline model); ii. Modelling variables that inherently vary over time as such (longitudinal model).

Results. A total of 571 patients were recruited and 439 (76.9%) completed 2-year follow-up. Failure of adherence to T2T-LDA was noted in 1765 (40.5%) visits. In the baseline multivariable model, high number of comorbidities (OR (95%CI): 1.10 (1.02; 1.19)), smoking (1.32 (1.08; 1.63)) and high number of tender joints (1.03 (1.02; 1.04)), were independently associated with failure to implement T2T, while ACPA/RF positivity (0.63 (0.50; 0.80)), was a significant facilitator of T2T. Results were similar in the longitudinal model.

Conclusions. Lack of adherence to T2T in the RA BIODAM cohort was evident in a

substantial proportion despite being a protocol requirement and this could be predicted by clinical features.

INTRODUCTION

Systematic reviews provide compelling evidence that treat-to-target (T2T) strategies lead to better results on any outcome which includes clinical, structural, functional, work productivity, comorbidity and costs, and irrespective of the precise nature of treatment and in both early and late RA[1-7]. This has led to the incorporation of this strategy in both ACR and EULAR treatment recommendations[8,9]. However, lack of adherence to the T2T strategy compromises achievement of optimal outcomes and leads to disease flares[10]. Knowledge regarding the factors that impede implementation and adherence to T2T, particularly in a setting where adherence to T2T is protocol specified, is limited.

The OMERACT Soluble Biomarker International Working Group initiated an international, multicenter, prospective study, RA BIODAM, aimed at setting a benchmark for the design, implementation, and analysis of studies aimed at the validation of prognostic parameters that are predictive of radiographic progression in RA. It was considered essential in the study design of a prospective cohort to include patients with a wide spectrum of disease activity receiving diverse treatments but adhering to a T2T strategy[11,12]. This would serve not only to optimize patient outcomes but also provide an opportunity to study the relationship between change in the candidate biomarker(s) related to treatment and subsequent change in the radiographic endpoint. The RA BIODAM study therefore provided an opportunity to assess adherence to the per-protocol T2T strategy over the course of the study and to identify patient and disease characteristics that could serve as barriers and facilitators of implementation of T2T.

METHODS

Study Design of RA BIODAM

This is a multi-center, multi-national, prospective observational study of patients with RA and fulfilling the 2010 Rheumatoid Arthritis Classification Criteria[13] recruited consecutively from rheumatologist outpatient clinics and offices in Canada (n=9), the USA (n=5), Israel (n=1), and Europe (Denmark (n=1), France (n=6), Germany (n=4), Ireland (n=1), Italy (n=6), the Netherlands (n=4), Norway (n=1)) (Trial Registration**:**

Assess Structural Damage in Rheumatoid Arthritis Using Biomarkers and Radiography: Clinicaltrials.gov #: NCT01476956, https://clinicaltrials.gov/ct2/show/NCT01476956, Registered June 1 2011). First patient was recruited October 30 2011 and last patient visit was May 17 2017. Details of the study design, inclusion and exclusion criteria, have been described in the first study report[14]. The study recruited patients who were starting csDMARD therapy or changing csDMARD therapy defined as an increase in dose of methotrexate by ≥5 mg weekly to a maximum dose of 25mg weekly, add-on of an alternative csDMARD, switch to an alternate csDMARD, or a TNFi was to be added to csDMARD therapy.

Disease activity was monitored systematically every 3 months using the DAS44. Changes in csDMARD and/or TNFi therapy were to be implemented according to 2010 EULAR recommendations which recommend a target of remission (REM) (DAS44 <1.6) for patients receiving csDMARD therapy in the setting of early disease (<2 years disease duration) and a target of low disease activity state (LDA) (DAS44 ≤2.4) for patients receiving TNFi in the setting of established disease and prior exposure to csDMARDs[15]. If treatment change was not implemented according to the protocol procedure, a study query was sent to the investigator requesting the reason for not adhering to T2T and one of the following options was provided for a response: patient decision (with specification), physician decision-concern regarding adverse event, physician decision-current treatment acceptable, physician decision-other (with specification), other, unspecified.

The study fulfilled Good Clinical Practice Guidelines, complied with the Declaration of Helsinki, and received ethical approval from the local ethics committee (cf appendix) and all patients provided written informed consent.

Statistical Analysis

Since rheumatologist adherence to a T2T treatment strategy was a key protocol-specified requirement we assessed the number of visits where this was not implemented. Failure to follow T2T according to a remission/low disease activity target (T2T-REM/LDA according to DAS44) was defined as: i) Failure to intensify treatment if REM/LDA status had *not* been attained, ii) Treatment intensification if REM/LDA status *had* been attained.

The following predictors were assessed to identify those factors associated with failure to implement T2T: clinical and socio-economic variables: age (years); gender (female/male); disease duration (years); country (each patient nested within country) and site type (academic/community); number of comorbidities (continuous); education (years); smoking status (current smoker/not current smoker); RF (positive/negative); ACPA (positive/negative); baseline medication status (csDMARDs naïve / csDMARDs experienced); number of previous DMARDs (continuous); treatment with bDMARDs /csDMARDs (dummy variable with 4 levels: reference: csDMARDs only); treatment with oral steroids (yes/no); HAQ (continuous). Disease activity variables: SJC (0-44); TJC (0-53); ESR (mm/h); CRP (mg/L); Patient global assessment (0-10); Physician global assessment (0-10).

We used 2-level binomial generalized estimating equations (GEE) models to test associations between potential predictors and failure to implement T2T-LDA (the primary outcome) and T2T-REM. Patients with at least 2 time points with available data were included in our models. Two types of models were created: A. Baseline model (only with baseline time-fixed variables); and B. Longitudinal model (with both time-fixed and time-varying -when appropriate variables). All variables were first tested in univariable models. Those with $p<0.20$ were selected for multivariable analysis. In the final model we used forward selection and included variables that were significantly associated with the outcome ($p<0.05$), taking collinearity into account. Repeated observations of the outcome over time and observations stemming from the same country were not assumed to be independent. The exchangeable working correlation structure was used to handle correlation between repeated measures (first level), and country was added as a covariate in all models to adjust for this higher level of correlation (second level).

Sensitivity Analyses

In addition to using DAS44 (main outcome, as per-protocol), we repeated all analyses using CDAI remission (≤2.8)/LDA (≤10) and SDAI remission (≤3.3)/LDA (≤11) to define failure to apply T2T (similar to the main analysis, only outcome differs), each in separate models.

RESULTS

Baseline Demographics and Disease Status.

Complete baseline data was available on 571 patients (4,427 visits) and 439 (76.9%) had complete 2-year follow-up. Reasons for discontinuation were: subject withdrew consent (52), subject lost to follow-up (25), major protocol violation(s) with study non-compliance (14), subject non-compliant with protocol (13), serious adverse event (10), other/unspecified (10), worsening of intercurrent medical condition (5), investigator judgment (3). Complete details of patient baseline characteristics are described in the RA BIODAM study report[14]. Overall, the patient population comprised a demographically typical cohort of patients with RA, the majority being female (76%) and with mean age of 55.7 years. Mean disease duration was 6.5 years and 52% had prior exposure to a csDMARD. Patients had active disease at baseline with a mean of 8.4 swollen joints, 13.6 tender joints, DAS28 of 5.2, DAS44 of 3.8, and CRP of 14.9 mg/L. The majority (77.7%) were either RF or ACPA positive.

Adherence to T2T

The percentage of patient visits where there was failure to adhere to T2T was relatively stable over time. In total, there was failure of adherence to a T2T-REM strategy in 1,765 (40.5%) of visits with the following reasons for this being provided in the eCRF: physician decision-current treatment acceptable (534 (30.3%)), physician decision-other (with specification) (93 (5.3%)), patient decision (with specification) (52 (2.9%)), other (40 (2.3%)), physician decision-concern regarding adverse event (22 (1.2%)), unspecified (1024 (58.0%)). There was failure of adherence to a T2T-LDA strategy in 1,098 (25.2%) of visits with the following reasons for this being provided in the eCRF: physician decision-current treatment acceptable (519 (47.3%)), physician decision-other (with specification) (93 (8.5%)), patient decision (with specification) (52 (4.7%)), physician decision-concern regarding adverse event (22 (2.0%)), other (38 (3.5%)), unspecified (374 (34.1%)). The number of patients for whom there was failure to adhere to T2T for one or more visits is provided in Figure 1. Failure to adhere to T2T was observed for a majority of patient visits (i.e. > 50% of all visits) in 70 (12.3%) of patients for T2T-REM and in 31(5.4%) of patients for T2T-LDA.

At the first 3-month follow up visit, failure of adherence to T2T-REM was evident in 46% of visits and for T2T-LDA this was 33%. Over the 2-year follow up there was a small decrease in the proportion of visits for which T2T-REM was not applied to 41% and a decrease for T2T-LDA to 20% of visits (Figure 2).

Main Analysis: Predictors of Failure to Implement T2T-REM

Older age and female gender were independent predictors of failure to implement T2T-REM in both the baseline and the longitudinal models (Tables 1 and 2). Higher level of education predicted a lower likelihood of failure to implement T2-REM (longitudinal models only). Among disease severity factors, a higher HAQ at baseline (but not during follow up) was associated with failure to implement T2T-REM, while ACPA positivity was associated with increased likelihood of implementing T2T-REM (only in the longitudinal models). For disease activity measures, higher number of tender joints both at baseline and during follow-up was associated with a lower likelihood of implementing T2T-REM while the number of swollen joints had the opposite effect (only longitudinal model).

Secondary Analysis: Predictors of Failure to Implement T2T-LDA

In contrast to the main analysis of T2T-REM, older age and female gender were not associated with failure to implement T2T-LDA and level of education also played no role (Tables 3 and 4). However, ACPA positivity was associated with increased likelihood of implementing T2T-LDA as also noted for T2T-REM. In contrast to the analysis of T2T-REM, higher number of comorbidities and smoking were independent predictors of failure to implement T2T-LDA while being in an academic centre was associated with an increased likelihood of implementing T2T-LDA (only in longitudinal model). Higher tender joint count was associated with failure to implement T2T-LDA but there was no independent impact of swollen joint count.

Sensitivity analyses

The results of all sensitivity analyses are similar to the ones from the main analysis and are shown in detail in Supplementary Tables S1-S2.

DISCUSSION

Our data shows that over the 2-year follow up with 3-monthly visits there was a lack of implementation of the protocol-specified T2T treatment strategy in 40% of the visits, this being due mainly to physician decision that treatment was acceptable amongst the specified reasons. There was a small decrease over 2 years in the proportion of visits for which implementation of treatment intensification aimed at T2T-remission was not applied although for T2T-LDA the proportion gradually decreased from 33% to 20%. Analysis of predictors of adherence to the T2T strategy suggests potential gaps in the care of female patients and smokers and demonstrates the value placed by rheumatologists on clinical biomarkers of prognosis to guide treatment decisions and their hesitancy in escalating treatment in the absence of definitive physical findings of synovitis.

It is now widely accepted that attaining stringent clinical remission is associated with optimal outcomes in RA[16-21]. A major challenge for T2T is its implementation because of insufficient adherence and persistence, which leads to flares and increased disease activity[10,22,23]. Physicians raise concerns regarding the time expended on systematic joint assessments, possibility for adverse events, costs of therapy, and discordance between their own assessments of the level of disease activity and the values provided by composite disease activity measures, particularly in the setting of damaged and tender joints and concomitant conditions such as osteoarthritis and fibromyalgia[24-26]. Consequently, low disease activity has also been proposed as a valuable alternative target, especially in established disease, as targeting low disease activity also leads to acceptable outcomes[27].

A recent report described T2T protocol adherence in The BeST-study (Dutch acronym for treatment strategies), a multicenter, randomized, clinical trial started in 2000 in the Netherlands, when T2T was not daily practice[28]. The aim was to evaluate the efficacy of four treatment strategies in 508 early active RA defined according to the 1987 American College of Rheumatology (ACR) criteria. The DAS was measured every 3 months and this was used to inform treatment decisions targeted at low disease activity (DAS44 $\leq$2.4)

by the rheumatologist. Protocol adherence to a T2T strategy in BeST was compared with adherence to T2T in the IMPROVED-study (acronym for Induction therapy with MTX and prednisone in rheumatoid or very early arthritic disease), which was also a multicenter, randomized, clinical trial started in the Netherlands in 2007 and including some of the centers that participated in the BeST study[27]. This recruited 479 early RA patients defined according to the 2010 ACR-EULAR) classification criteria and 122 undifferentiated arthritis patients, who started induction therapy with MTX and tapered high dose prednisone followed by 4-monthly treatment targeted at DAS44-remission (<1.6). Protocol adherence decreased over time in both studies, more so in the DAS <1.6 targeted study, and was 80% in BeST and 60% in IMPROVED at 2 years follow up. In both studies, violations were associated with rheumatologists' disagreement with how the measured DAS represented actual disease activity, or with the next treatment step. These data are similar to what we report for protocol adherence in the RA-BIODAM cohort. Following a protocol that aims at a stricter treatment target is more difficult because it may be perceived as conveying no additional clinical benefit, and enhancing risks of side effects and/or higher costs. Rheumatologists have reported that they feel the measured DAS overestimates actual disease activity in a DAS <1.6-steered treatment protocol compared to a DAS ≤2.4-steered treatment protocol[29]. The COBRA study also aimed treatment decisions to attain DAS-remission and showed comparable protocol violations during 6 months follow-up (24 %)[30]. In a 3-year retrospective follow up of Australian patients with RA who were DMARD naïve, had disease duration of less than 1 year, and had treatment intensification according to DAS28 assessment, deviation from protocol occurred in 30.6%, 29.0%, and 32.3% in the periods 6 to 12, 12 to 24 and 24 to 36 months after treatment initiation, respectively[31].

A significant difference of this past experience with T2T strategic decision-making compared to the RA-BIODAM cohort is that adherence to a treatment strategy based on T2T-LDA substantially improved over time, which could reflect a process of enhanced awareness to follow T2T made possible by an alert mechanism built into the RA-BIODAM eCRF platform. This simple tool could be integrated into an electronic medical record suggesting a potential solution for enhancing best practices in the treatment of RA. It is also possible that the more flexible and a greater number of options for treatment

change in RA-BIODAM facilitated adherence to a T2T strategy as compared to the studies that were conducted earlier than RA-BIODAM.

In the longitudinal analysis of predictors of failure to implement a T2T strategy, differences were found when using a strategy based on targeting remission or low disease activity (both according to DAS44). A higher number of swollen joints during follow-up were associated with increased implementation of T2T-REM while a higher number of tender joints had the opposite effect, both at baseline and during follow-up. This finding supports the view that treatment targeted to remission is strongly driven by the importance attached by rheumatologists to eliminating inflammation in swollen joints. The higher the score of this objective sign of inflammation (irrespective of CRP/ESR), the higher the likelihood that rheumatologists will decide on more 'aggressive' treatment strategies. Being ACPA positive was also associated with a greater likelihood that the T2T strategy would be implemented. Rheumatologists might feel more confident to implement strict treatment strategies in cases where they also feel more confident in the diagnosis. In addition, ACPA positivity is a known adverse prognostic factor, so rheumatologists appear to take into account prognostic factors when deciding to follow T2T or not, and follow it more in the presence of ACPA positivity. A limitation of the anti-CCP test is that it is relatively invariant to change over time and that is why it is not assessed in a prospective manner. Additional prognostic biomarkers that are modifiable and could be targeted for treatment intervention therefore represent a major unmet need in the optimal management of RA, which reinforces the rationale for the development of the RA BIODAM cohort because this may ultimately enhance the adoption of T2T strategies in real world practice.

Several demographic variables influenced implementation of T2T. In particular, we found that older age and female gender were associated with a lower likelihood of implementing T2T-REM both in models with only time-fixed variables (baseline model) and in longitudinal models also incorporating time-varying variables. But interestingly, this association was not found when modeling T2T-LDA. Potential reasons for lack of implementation of T2T towards a target of remission in older individuals could be concern regarding adverse events, difficulty in distinguishing inflammatory from degenerative joint pain, and comorbidities that result in a more conservative approach to

therapy. The less intensive treatment approach adopted in women is disconcerting and requires further study as to causal factors and the impact on attainment of remission and prevention of joint damage. Higher level of education was also found to be associated with higher likelihood of implementation of T2T-REM (but not T2T-LDA). More educated patients may be more proactive in finding information about optimal management of RA. Heightened awareness of the impact of inflammation on joint damage and even information about T2T strategies as the optimal mode of treatment may persuade patients to accept treatment intensification. A higher number of comorbidities and being a current smoker were independently associated with higher likelihood to fail to apply T2T-LDA (not T2T-REM). Rheumatologists may be concerned about adverse events and interaction with other therapies in such patients, which could lead them to be more conservative in implementing aggressive treatment strategies. The association between higher HAQ (more disability) and higher likelihood to fail T2T was also seen in the baseline model for T2T-REM. Previous reports of factors accounting for protocol deviations in T2T studies have similarly cited comorbidity, drug toxicity, and patient-reported factors such as helplessness, mHAQ, pain, and fatigue[32-37]. Body mass index, baseline DAS28, and tender joint count were also associated with the number of deviations.

The outcomes used in this analysis incorporate treatment decisions, and thus reflect the rheumatologists' perceptions about T2T. We have observed that rheumatologists in the RA BIODAM study went outside protocol and decided based on their best knowledge what to do in each case. On the one hand this informs us (or better, confirms) that confounding by indication is present in RA BIODAM, but also indicates that this cohort is truly reflecting how RA patients are treated in daily clinical practice. Keeping this in mind, this analysis sheds light into what is perceived by rheumatologists as facilitators and barriers when deciding to apply T2T in clinical practice. Having a high number of swollen joints, being ACPA positive and being more educated were found to be facilitators. On the contrary, older age, female gender, high number of tender joints, high baseline HAQ, high number of comorbidities, and being a smoker were perceived by rheumatologists as barriers to implementation of T2T.

In conclusion, despite a protocol specific requirement to adhere to a T2T treatment strategy this was not implemented in 40% of patient visits for the DAS44 remission target and in 25% for the DAS44 LDA target, although there was a steady decline in DAS44 LDA failures over the 2-year follow up. Rheumatologists are influenced by objective measures such as swollen joints and positivity for ACPA in deciding on implementation of treatment intensification due to their association with prognosis. The validation of modifiable biomarkers of RA prognosis using the resources generated in RA BIODAM may therefore provide rheumatologists with additional tools that will facilitate decision-making in clinical practice.

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References

1. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis 2016; 75:16–22.
2. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, 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; 71:845–850.
3. Schipper LG, van Hulst LT, Grol R, van Riel PL, Hulscher ME, Fransen J. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology (Oxford) 2010; 49:2154–2164.
4. Pope JE, Haraoui B, Rampakakis E, Psaradellis E, Thorne C, Sampalis JS, et al. Optimization of Adalimumab Trial Investigators. Treating to a target in established active rheumatoid arthritis patients receiving a tumor necrosis factor

inhibitor: results from a real-world cluster-randomized adalimumab trial. Arthritis Care Res (Hoboken) 2013; 65:1401–1409.

5. Vermeer M, Kievit W, Kuper HH, Braakman-Jansen LM, Bernelot Moens HJ, et al. Treating to the target of remission in early rheumatoid arthritis is cost-effective: results of the DREAM registry. BMC Musculoskelet Disord 2013; 14:350.
6. Provan SA, Semb AG, Hisdal J, Stranden E, Agewall S, Dagfinrud H, et al. Remission is the goal for cardiovascular risk management in patients with rheumatoid arthritis: a cross-sectional comparative study. Ann Rheum Dis 2011; 70:812–817.
7. Jurgens MS, Welsing PM, Geenen R, Bakker MF, Schenk Y, de Man YA, et al. The separate impact of tight control schemes and disease activity on quality of life in patients with early rheumatoid arthritis: results from the CAMERA trials. Clin Exp Rheumatol 2014; 32:369–376.
8. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014; 73:492–509.
9. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2016; 68:1–26.
10. Kuusalo L, Puolakka K, Kautiainen H, Blafield H, Eklund KK, Ilva K, et al. Impact of physicians' adherence to treat-to-target strategy on outcomes in early rheumatoid arthritis in the NEORACo trial. Scand J Rheumatol 2015; 44:449–55.
11. Maksymowych WP, Landewe R, Tak PP, Ritchlin CJ, Ostergaard M, Mease PJ,et al. Reappraisal of OMERACT 8 draft validation criteria for a soluble biomarker reflecting structural damage endpoints in rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis: The OMERACT 9 v2 criteria. J Rheumatol 2009; 36: 1785-91.
12. Maksymowych WP, Fitzgerald O, Wells GA, Gladman DD, Landewe R, Ostergaard M, et al. Proposal for levels of evidence schema for validation of a

soluble biomarker reflecting damage endpoints in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, and recommendations for study design. J Rheumatol 2009; 36: 1792-9.

13. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid Arthritis Classification Criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheum 2010; 62: 2569–81.
14. Maksymowych WP, FitzGerald O, Østergaard M, Homik J, van der Heijde D, Lambert RG, et al. The International RA BIODAM Cohort for validation of soluble biomarkers in rheumatoid arthritis. J Rheumatol (submitted)
15. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010; 69: 631–7.
16. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011; 70:404–413.
17. Kavanaugh A, Fleischmann RM, Emery P, Kupper H, Redden L, Guerette B, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. Ann Rheum Dis 2013; 72:64–71.
18. Sakellariou G, Scire CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Ann Rheum Dis 2013; 72:245–249.
19. Thiele K, Huscher D, Bischoff S, Spathling-Mestekemper S, Backhaus M, Aringer M, et al. Performance of the 2011 ACR/EULAR preliminary remission criteria compared with DAS28 remission in unselected patients with rheumatoid arthritis. Ann Rheum Dis 2013; 72:1194–1199.

20. Radner H, Smolen JS, Aletaha D. Remission in rheumatoid arthritis: benefit over low disease activity in patient reported outcomes and costs. Arthritis Res Ther 2014; 16:R56.
21. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016; 75:3–15.
22. Pascual-Ramos V, Contreras-Yanez I, Villa AR, Cabiedes J, Rull-Gabayet M. Medication persistence over 2 years of follow-up in a cohort of early rheumatoid arthritis patients: associated factors and relationship with disease activity and with disability. Arthritis Res Ther 2009; 11:R26.
23. Contreras-Yanez I, Pascual-Ramos V. Window of opportunity to achieve major outcomes in early rheumatoid arthritis patients: how persistence with therapy matters. Arthritis Res Ther 2015; 17:177.
24. Haraoui B, Smolen JS, Aletaha D, Breedveld FC, Burmester G, Codreanu C, et al. Treating rheumatoid arthritis to target: multinational recommendations assessment questionnaire. Ann Rheum Dis 2011; 70:1999–2002.
25. Markusse IM, Dirven L, Han KH, van Groenendael JH, Ronday HK, Kerstens PJ, et al. Evaluating adherence to a treat-to-target protocol in recent-onset rheumatoid arthritis: reasons for compliance and hesitation. Arthritis Care Res (Hoboken) 2015; 68: 446–453
26. Bakker MF, Jacobs JW, Verstappen SM, Bijlsma JW. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007; 66 (Suppl 3):iii56–iii60.
27. Bergstra SA, Olivas O, Akdemir G, Riyazi N, Collée G, van Groenendae JHLM, 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.
28. Akdemir G, Markusse IM, Goekoop-Ruiterman YPM, Steup-Beekman GM, Grillet BAM, Kerstens PJSM, et al. Rheumatologists' adherence to a disease activity score steered treatment protocol in early arthritis patients is less if the target is remission. Clin Rheumatol 2017; 36:317–326.

29. Wolfe F, Michaud K, Pincus T, Furst D, Keystone E. The disease activity score is not suitable as the sole criterion for initiation and evaluation of anti-tumor necrosis factor therapy in the clinic: discordance between assessment measures and limitations in questionnaire use for regulatory purposes. Arthritis Rheum 2005; 52: 3873-9.
30. den Uyl D, terWee M, Boers M, Kerstens P, Voskuyl A, Nurmohamed M, et al. A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. Ann Rheum Dis 2014; 73:1071-8.
31. Wabe N, Sorich MJ, Wechalekar DM, Cleland LG, McWilliams L, Lee A, et al. Characterising deviation from treat-to-target strategies for early rheumatoid arthritis: the first three years. Arthritis Res Ther 2015; 17:48.
32. Tymms K, Zochling J, Scott J, Bird P, Burnet S, de Jager J, et al. Barriers to optimal disease control for rheumatoid arthritis patients with moderate and high disease activity. Arthritis Care Res 2014; 66: 190–6.
33. Vermeer M, Kuper HH, Bernelot Moens HJ, et al. Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the DREAM remission induction cohort. Arthritis Res Ther 2012;14: R254.
34. Wolfe F, Michaud K. Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. Arthritis Rheum 2007; 56: 2135–42.
35. Barton JL, Imboden J, Graf J, et al. Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2010; 62: 857–64.
36. Nicolau G, Yogui MM, Vallochi TL, et al. Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. J Rheumatol 2004; 31: 1293–6.
37. Pincus T, Esther R, DeWalt DA, Callahan LF. Social condition and self-management are more powerful determinants of health than access to care. Ann Intern Med 1998; 129: 406–11.

Figure Legends.

1. Failure of adherence to a T2T treatment strategy according to the number of visits per patient assessed every 3 months over 2 years in the RA BIODAM cohort. A: T2T according to DAS44 remission); B: T2T according to DAS44 LDA. T2T, treat-to-target; RA, rheumatoid arthritis; REM, remission; LDA, low disease activity. Note: x-axis represents the number of visits where T2T was not applied; for instance in Figure 1A, in 79 patients, rheumatologists failed to apply T2T-REM in 4 visits [total 79*4=316; which corresponds to 17.9% of all (N=1,765) visits where T2T-REM was not applied].

2. Proportion of patients failing to follow T2T per visit. In total rheumatologists failed to appropriately apply the T2T-REM approach in 1,765 visits (40.5%) and the T2T-LDA approach in 1,098 visits (25.2%).

APPENDIX

Ethics approval and consent to participate

All patients included in this study provided written informed consent. The study was approved by the following local medical ethical committees:

Investigator	Ethics Board	Approval/Reference No.
Cheryl Barnabe	University of Calgary Conjoint Health Research Ethics Board	Ethics ID: E-24487
Gilles Boire	Comité d'éthique de la recherche en santé chez l'humain du Centre hospitalier universitaire de Sherbrooke	Pour le projet # 11-069
Carol Hitchon	University of Manitoba Bannatyne Campus Health Research Ethics Board	Ref No: H2011:177
Joanne Homik	University of Alberta Health Research Ethics Board	Pro00020927
Maggie Larché	Hamilton Integrated Research Ethics Board	Project # 12-3691
Proton Rahman	Health Research Ethics Authority of Newfoundland & Labrador	Ref # 11.351

Saeed Shaikh	Institutional Review Board Services	N/A
Carter Thorne	Southlake Regional Health Centre Research Ethics Board	SRHC# 0020-1112
Mikkel Østergaard	De Videnskabsetiske Komiteer i Region Hovedstaden	H-4-2011-085
Bernard Combe (National Approval)	Comité de Protection des Personnes Sud-Méditerranée IV	National PI Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
Alain Cantagrel	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
Maxime Dougados	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
René-Marc Flipo	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38 ; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
Alain Saraux	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40

Thierry Schaeverbeke	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
Marina Backhaus/ Gerd Burmester	Ethikausschuss 1 am Campus Charité - Mitte	Application No: EA1/255/11
Thomas Neumann	Universitätsklinikum Jena Ethik-Kommission	Bearbeitungs Nr: 3466-06/12
Wolfgang Spieler	Die Ethikkomission der Ärztekammer Sachen-Anhalt	23/12
Ingo Tarner	Ethik-Kommission am Fachbereich Medizin Justus -Liebig Universität Giessen	AZ: 40/12
Oliver FitzGerald	St. Vincent's Healthcare Group Limited Ethics and Medical Research Committee	N/A
Ori Elkayam	Tel Aviv Sourasky Medical Center Institutional Review Board (Helsinki Committee)	0146-11-TLV
Gianfranco Ferraccioli	Università Cattolica Del Sacro Cuore Facoltà di Medicina E Chirurgia "Agostino Gemelli" Comitato Ethico	Prot If (A.1135)/C.E./2011; p/797/CE 2011
Maurizio Rossini	Azienda Ospedaliera Universitaria Integrata Verona Dipartimento Direzione Medica Ospedaliera e Farmacia Comitato Etico Per La Sperimentazione	Sperimentazione n. prog. CE 2156
Leonardo Punzi	Regione Veneto Azienda Ospedaliera di Padova Comitato Etico per la Sperimentzione	Prot. N. 2554P
Marcello Govoni	Comitato Etico Della Provincia Di Ferrara	Protocollo n. 118-2011
Piercarlo Sarzi-Puttini	Ospedale Luigi Sacco, Azienda Ospedaliera - Polo Universitario, Comitato Etico Locale ET/nb	Prot. N. 272/2012/20/AP
Luigi Sinigaglia	Azienda Ospedaliera, Istituto Ortopedico Gaetano Pini, Comitato Etico	4/2011
Robert Landewé	Medisch Ethische ToetsingsCommissie van Zuyderland én van Zuyd Hogeschool	Ref: MECT 11-T-98; Ref: NL38200.096.11
Renée Allaart	Leids Universitair Medisch Centrum Commissie Medische Ethiek	Ref: METC 11-T-98; Ref: NL38200.096.11; Ref: P12.049/SH/sh

Paul-Peter Tak	Medisch Ethische Commissie, Academisch Medisch Centrum Universiteit van Amsterdam	METC 12-015
Dirkjan van Schaardenburg	Leids Universitair Medisch Centrum, Commissie Medische Ethiek, Medisch Ethische Eoetsingscommissie, voor het Slotervaartziekenhuis en Reade	Ref: MECT 11-T-98; Ref: NL38200.096.11; Nummer: U/12.014/P1204
Hilde Berner Hammer	REK Regionale Komiteer for Medisinsk Og Helsefaglig Forskningsetikk	Ref: 2011/1338
Clifton Bingham	Johns Hopkins Medicine Institutional Review Boards	Study #: NA_00052505
Philip Mease	Western Institutional Review Board (WIRB)	Study Num: 1128284; WIRB Pro Num: 20111712
Joan Bathon	Columbia University Medical Center Institutional Review Board	Protocol Number: IRB-AAAI4651
Christopher Ritchlin	University of Rochester Research Subjects Review Board	RSRB: RSRB00039665
Vivian Bykerk	Institutional Review Board of the Hospital for Special Surgery	2014-228-CR2

N/A An ethics approval number is not provided by these ethics committees

Availability of data and materials

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

Three different databases were developed by the coordinating project management group CARE Arthritis, which were linked by the patient study ID:

1. Clinical database: clinical data was recorded in the RA BIODAM eCRF, and an interactive system of study queries was used to proactively verify data entry and address missing data within prespecified time frames.
2. Biosample biorepository: aliquoted sera, urine, and RNA biosamples were barcoded and stored at -70C.
3. Imaging repository: all anonymized DICOM radiographs of hands and feet passed quality assurance procedures.

Access to all RA BIODAM data and biosamples will be made available for academic and not-for profit entities. This will require the submission of a study proposal to the scientific committee, which can be found at www.carearthritis.com.

Authors' contributions

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.

Table 1. Baseline model: Baseline predictors of failure to apply T2T-REM during 2-year follow-up in the RA BIODAM Cohort.

	Univariable OR (95% CI) (N=544-571)	Univariable p-value	Multivariable OR (95% CI) (N=549)
Age (years)	**1.01 (1.01; 1.02)**	**<0.001**	**1.01 (1.01; 1.02)**
Gender (female)	**1.36 (1.11; 1.66)**	**0.003**	**1.35 (1.11; 1.64)**
Disease duration (years)	1.01 (0.99; 1.02)	0.271	†
Education (years)	**0.96 (0.94; 0.98)**	**0.001**	¥
Number of comorbidities	**1.11 (1.04; 1.19)**	**0.003**	¥
Current smoker	1.07 (0.90; 1.28)	0.418	†
Type of centre (academic)	1.01 (0.85; 1.20)	0.935	†
RF positivity	0.89 (0.74; 1.08)	0.233	†
ACPA positivity	**0.81 (0.68; 0.97)**	**0.024**	¥
RF and/or ACPA positivity	0.85 (0.69; 1.05)	0.136	¥
PGA (0-10)	**1.07 (1.03; 1.11)**	**<0.001**	¥
PhGA (0-10)	1.02 (0.98; 1.07)	0.351	†
Swollen joint count (0-44)	1.00 (0.99; 1.02)	0.514	†
Tender joint count (0-53)	**1.02 (1.01; 1.03)**	**<0.001**	**1.01 (1.01; 1.02)**
ESR (mm/h)	1.00 (1.00; 1.01)	0.161	¥
CRP (mg/L)	1.00 (0.99; 1.00)	0.235	†
HAQ	**1.40 (1.25; 1.57)**	**<0.001**	**1.27 (1.12; 1.44)**
Number of previous csDMARDs	**1.07 (1.00; 1.15)**	**0.057**	¥
Previous treatment with any csDMARD	**1.19 (1.01; 1.40)**	**0.041**	¥

†: not selected from the univariable analysis (p>0.20); ¥: not significant in the multivariable analysis (p>0.05). Country added as a covariate in all univariable models and in the final multivariable model. Final model also adjusted for type of treatment (csDMARDs and/or bDMARDs)

Table 2. Longitudinal model: Time-fixed and Time-varying predictors of failure to apply T2T-REM during 2-year follow-up in the RA BIODAM cohort.

	Univariable OR (95% CI) (N=544-571)	Univariable p-value	Multivariable OR (95% CI) (N=545)
Age (years)	**1.01 (1.01; 1.02)**	**<0.001**	**1.01 (1.00; 1.02)**
Gender (female)	**1.36 (1.11; 1.66)**	**0.003**	**1.43 (1.15; 1.77)**
Disease duration (years)	1.01 (0.99; 1.02)	0.271	†
Education (years)	**0.96 (0.94; 0.98)**	**0.001**	**0.97 (0.94; 0.99)**
Number of comorbidities	**1.11 (1.04; 1.19)**	**0.003**	¥
Current smoker	1.07 (0.90; 1.28)	0.418	†
Type of centre (academic)	1.01 (0.85; 1.20)	0.935	†
RF positivity	0.89 (0.74; 1.08)	0.233	†
ACPA positivity	**0.81 (0.68; 0.97)**	**0.024**	**0.79 (0.65; 0.95)**
RF and/or ACPA positivity	0.85 (0.69; 1.05)	0.136	¥
PGA (0-10) ‡	1.00 (0.97; 1.03)	0.966	†
PhGA (0-10) ‡	**0.91 (0.89; 0.94)**	**<0.001**	¥
Swollen joint count (0-44) ‡	**0.93 (0.91; 0.95)**	**<0.001**	**0.92 (0.90; 0.94)**
Tender joint count (0-53) ‡	**0.99 (0.98; 1.00)**	**0.002**	**1.02 (1.00; 1.03)**
ESR (mm/h) ‡	1.00 (1.00; 1.00)	0.878	†
CRP (mg/L) ‡	**0.99 (0.98; 0.99)**	**0.003**	¥
HAQ ‡	1.03 (0.91; 1.15)	0.681	†
Number of previous csDMARDs	1.07 (1.00; 1.15)	0.057	¥
Previous treatment with any csDMARD	**1.19 (1.01; 1.40)**	**0.041**	¥

†: not selected from the univariable analysis (p>0.20); ¥: not significant in the multivariable analysis (p>0.05); ‡ modelled as time-varying. Country added as a covariate in all univariable models and in the final multivariable model. Final model also adjusted for type of treatment (csDMARDs and/or bDMARDs)

Table 3. Baseline model: Baseline predictors of failure to apply T2T-LDA during 2-year follow-up of the RA BIODAM Cohort.

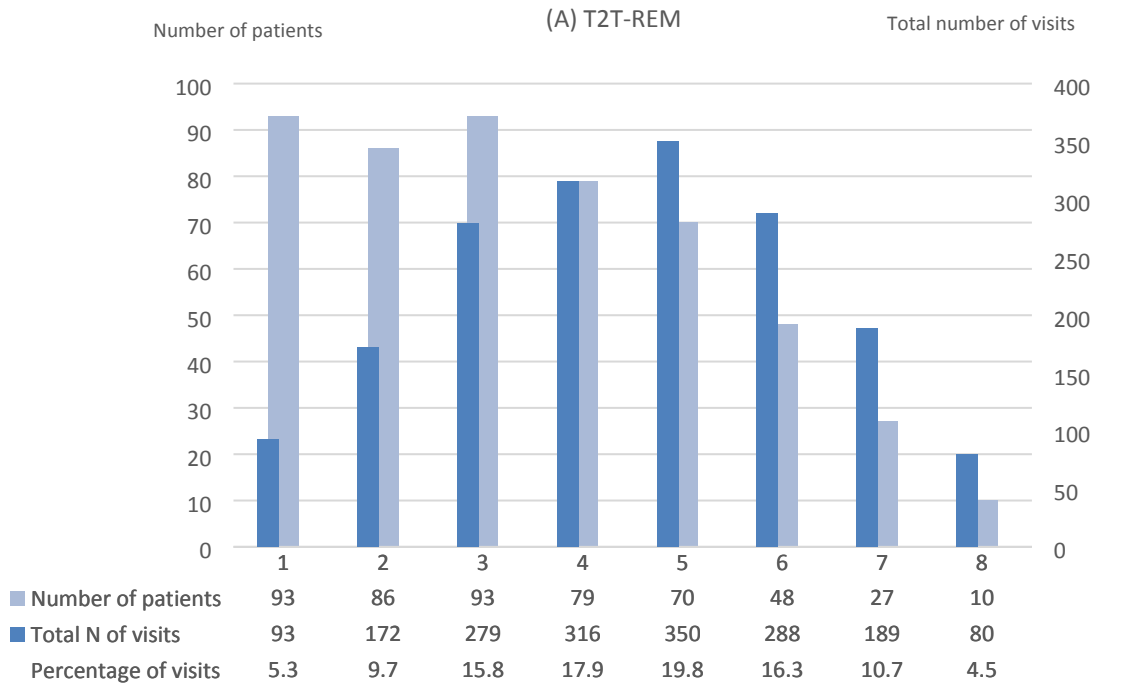
	Univariable OR (95% CI) (N=544-571)	Univariable p-value	Multivariable OR (95% CI) (N=549)
Age (years)	**1.01 (1.00; 1.01)**	**0.096**	¥
Gender (female)	1.01 (0.81; 1.25)	0.963	†
Disease duration (years)	1.00 (0.99; 1.02)	0.528	†
Education (years)	**0.97 (0.95; 1.00)**	**0.032**	¥
Number of comorbidities	**1.17 (1.08; 1.26)**	**<0.001**	**1.10 (1.02; 1.19)**
Current smoker	**1.24 (1.01; 1.53)**	**0.041**	**1.32 (1.08; 1.63)**
Type of centre (academic)	**0.82 (0.67; 1.00)**	**0.050**	**0.81 (0.66; 0.99)**
RF positivity	**0.63 (0.51; 0.77)**	**<0.001**	£
ACPA positivity	**0.57 (0.47; 0.70)**	**<0.001**	£
RF and/or ACPA positivity	**0.58 (0.46; 0.73)**	**<0.001**	**0.63 (0.50; 0.80)**
DAS44 ESR LDA	1.06 (0.58; 1.96)	0.845	†
PGA (0-10)	**1.07 (1.03; 1.12)**	**0.001**	¥
PhGA (0-10)	**1.07 (1.02; 1.13)**	**0.009**	¥
Swollen joint count (0-44)	1.01 (1.00; 1.03)	0.075	¥
Tender joint count (0-53)	**1.03 (1.03; 1.04)**	**<0.001**	**1.03 (1.02; 1.04)**
ESR (mm/h)	1.00 (1.00; 1.01)	0.516	†
CRP (mg/L)	1.00 (0.99; 1.00)	0.908	†
HAQ	**1.29 (1.12; 1.49)**	**<0.001**	¥
Number of previous csDMARDs	1.02 (0.94; 1.11)	0.622	†
Previous treatment with any csDMARD	1.10 (0.91; 1.33)	0.318	†

†: not selected from the univariable analysis (p>0.20); ¥: not significant in the multivariable analysis (p>0.05); £: RF or ACPA positivity entered into multivariate model. Country added as a covariate in all univariable models and in the final multivariable model. Final model also adjusted for type of treatment (csDMARDs and/or bDMARDs)

Table 4. Longitudinal model: Time-fixed and Time-varying predictors of failure to apply T2T-LDA during 2-year follow-up of the RA BIODAM cohort.

	Univariable OR (95% CI) (N=544-571)	Univariable p-value	Multivariable OR (95% CI) (N=554)
Age (years)	**1.01 (1.00; 1.01)**	**0.096**	¥
Gender (female)	1.01 (0.81; 1.25)	0.963	†
Disease duration (years)	1.00 (0.99; 1.02)	0.528	†
Education (years)	**0.97 (0.95; 1.00)**	**0.032**	¥
Number of comorbidities	**1.17 (1.08; 1.26)**	**<0.001**	**1.11 (1.03; 1.20)**
Current smoker	**1.24 (1.01; 1.53)**	**0.041**	**1.26 (1.03; 1.53)**
Type of centre (academic)	**0.82 (0.67; 1.00)**	**0.050**	**0.81 (0.68; 0.98)**
RF positivity	**0.63 (0.51; 0.77)**	**<0.001**	£
ACPA positivity	**0.57 (0.47; 0.70)**	**<0.001**	£
RF and/or ACPA positivity	**0.58 (0.46; 0.73)**	**<0.001**	**0.66 (0.53; 0.82)**
PGA (0-10) ‡	**1.11 (1.08; 1.14)**	**<0.001**	¥
PhGA (0-10) ‡	**1.06 (1.03; 1.10)**	**<0.001**	¥
Swollen joint count (0-44) ‡	1.00 (0.98; 1.02)	0.962	†
Tender joint count (0-53) ‡	**1.03 (1.03; 1.04)**	**<0.001**	**1.02 (1.01; 1.03)**
ESR (mm/h) ‡	**1.01 (1.00; 1.01)**	**0.013**	¥
CRP (mg/L) ‡	1.00 (0.99; 1.00)	0.453	†
HAQ ‡	**1.43 (1.26; 1.61)**	**<0.001**	¥
Number of previous csDMARDs	1.02 (0.94; 1.11)	0.622	†
Previous treatment with any csDMARD	1.10 (0.91; 1.33)	0.318	†

†: not selected from the univariable analysis (p>0.20); ¥: not significant in the multivariable analysis (p>0.05); ‡ modelled as time-varying; £: RF or ACPA positivity entered into multivariate model. Country added as a covariate in all univariable models and in the final multivariable model. Final model also adjusted for type of treatment (csDMARDs and/or bDMARDs)



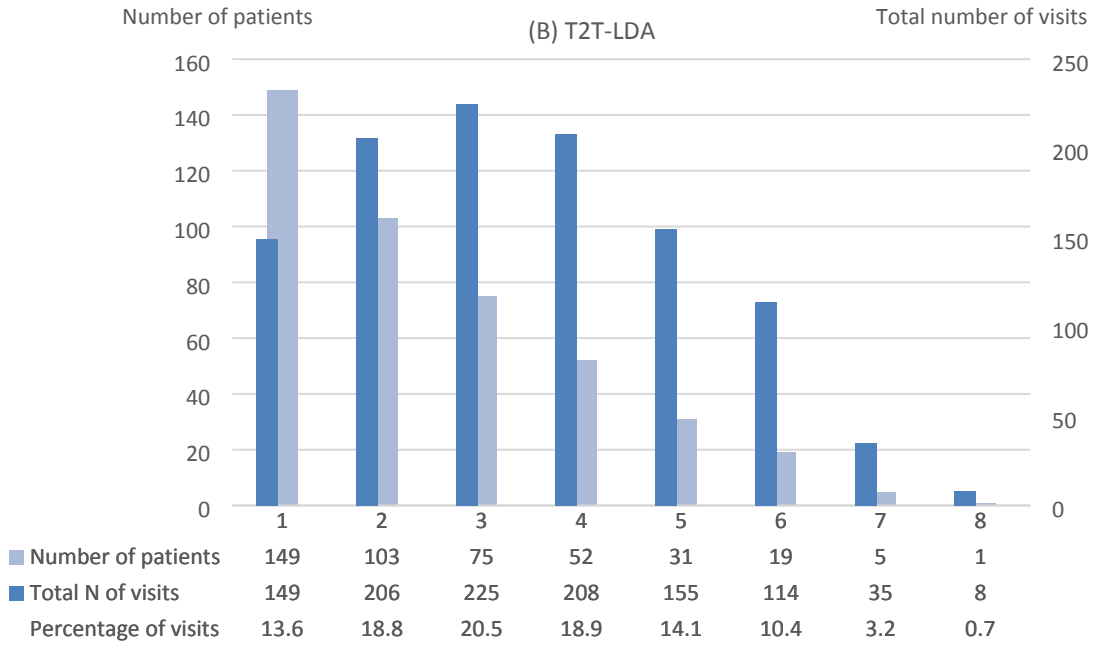


Figure 1.

Figure 2.