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Original Article

Treat-to-target concept implementation for evaluating rheumatoid arthritis patients in daily practice

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Abstract

Objective: We aimed to assess the implementation of the treat-to-target (T2T) concept in rheumatoid arthritis (RA) patients in daily practice.

Methods: All RA patients visiting one of the 7 academic medical centers in Israel in June 2015 with at least 3 previous clinic visits were included in this study. A common questionnaire was used to collect data from patients' medical records, and two independent rheumatologists evaluated the collected data for the implementation of the T2T concept. The associations between T2T implementation and the categorical and continuous variables were assessed.

Results: The study included 724 patients with a mean (standard deviation) age of 62.6 (13.97) years and 575 (80.4%) of them were women. Four centers used more than one scoring method, with Disease Activity Score-28 and Clinical Disease Activity Index) being most commonly used. Only 276 (38.1%) patients had disease score results in ≥3 visits, and the T2T recommendations were implemented for 245 (33.8%) of the 724 patients. The rate of implementation was higher in younger (p=0.028) rheumatoid factor-positive patients (p=0.011) and varied between centers (11.1%-87% p<0.0001). T2T implementation did not correlate to gender, place of residence, education, tobacco use, treatment regimens, and presence of erosions or comorbidities.

Conclusion: The T2T concept was implemented on only 33.8% of patients and was not affected by RA disease severity. Further studies are needed to determine the reasons for this deviation from the T2T standard of care for RA as well as its consequences.

Keywords: Treat to target (T2T), rheumatoid arthritis (RA), disease activity measures

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Introduction

Rheumatoid arthritis (RA), a chronic systemic inflammatory condition, affects 1% of the population. It is characterized by systemic inflammation of the joints with extraarticular manifestations involving multiple organ systems, such as the lungs, heart, and blood vessels, causing significant morbidity and mortality, and increasing costs (1). Joint damage and physical disability are the major adverse outcomes and are associated with reduced quality of life and premature mortality (1, 2).

Rheumatoid arthritis in the early stages has been known to be more sensitive to therapeutic intervention, with an early and good response being predictive of better long-term disease outcomes (4-6). The introduction of disease-modifying anti-rheumatic drug (DMARD) therapy has made remission or low disease activity an achievable goal in many patients (7-9). Therefore, the current RA treatment goals of achieving disease remission and preventing progressive joint damage rely on early, aggressive, and continuous interventions.

In several areas of medicine, including diabetes, hyperlipidemia, and hypertension, it has been consistently demonstrated that regular monitoring of the disease activity and subsequent adjustment of medication following a fixed protocol for achieving a predefined treatment goal is more beneficial than the conventional treatment. This approach has reliably been shown to reduce complications and organ damage in these conditions (10, 11). Based on this concept, an international task force first published its guidelines for the treat-to-target (T2T) approach in 2010 (12), which was updated in 2014 (13) to include 4 overarching principles and 10 recommendations. The updates were designed to tighten RA disease control in clinical practice by providing guidance for treating RA patients to a predefined target of low disease activity or

remission in both early and established RA (14-16). One of the overarching principles in T2T involves the implementation of quantifiable measures of disease activity, including tender and swollen joint counts, physician and/or patient global assessment, and laboratory tests indicative of active inflammation, which can be used to estimate disease activity in clinical practice. As the actual data regarding the extent of T2T implementation in daily clinical practice is limited mostly to physician surveys, we aimed to study the real-life adherence to the T2T concept. We conducted the present study to analyze the extent of implementation of T2T recommendations in RA management across Israel by determining the actual use of validated disease activity scores and the correlation between the recorded scores and treatment alteration.

Methods

Study population

The medical charts of RA patients who were ≥18 years of age and visited one of the 7 rheumatology clinics affiliated to the academic medical centers in Israel in June 2015 were screened and those with at least 3 previous clinic visits within a period of 12 months were included in the study. In Israel, a common national healthcare insurance plan is applicable to the entire population regardless of sex, ethnic background, religious affiliation, or socioeconomic status, and medical centers from all the geographic regions of the country. The RA diagnosis in the study patients was based on the 1987 American College of Rheumatology (ACR) criteria (17) or the 2010 ACR/European League Against Rheumatism (EULAR) criteria for the classification of RA (18). The study was approved by the Carmel Hospital Institutional Review Board of the individual medical centers. The requirement for individual patient consent form was waived due to the retrospective and observational nature of the study.

Data collection

In each medical center, patients were enrolled prospectively during their regular follow-up clinic visits in June 2015. An independent staff member who was not involved in direct patient care and blinded to the study goals and design was assigned to evaluate the charts retrospectively. The main inclusion criterion was that each patient had to have at least 3 previous clinic visits over the previous 12-month period from which relevant data could be collected for the study; the blinded staff member evaluated these clinic visit notes. Patient clinic visit notes were recorded in an electronic medical records system that freezes the data at the end of the day's visits, ensuring that no additional changes are made. The independent staff member was asked to collect data from these notes using a common questionnaire (Case Report Form [CRF]) considering the following parameters: patient demographics, including age, sex, ethnicity, place of residence, social history with level of education, current employment, and alcohol and tobacco use; presence of any comorbidities; and RA disease characteristics, such as age at disease onset, seropositivity (presence of rheumatoid factor [RF] and/or anti-cyclic citrullinated protein [anti-CCP]), the presence or absence of erosive disease, past and present use of synthetic and/or biologic DMARDs, non-steroidal antiinflammatory drug, and corticosteroids and their doses, presence of any medication side effects and drug-related adverse events, such as hospitalizations or infections, and patient treatment preferences in case these were specified by the treating rheumatologist. Importantly, the use of any of 4 disease activity scores, which were validated by ACR, for following disease activity in RA patients: Disease Activity Score (DAS)-28, Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI), or Routine Assessment of Patient Index Data 3 (RAPID-3) was noted. Each patient was then assigned a number code by which his/her CRF could be identified anonymously.

Data evaluation

All data collected in the CRFs were later evaluated by an independent committee composed of two practicing rheumatologists (OE and DZ) who were blinded to patient identification, treating physicians, and the medical center from which each CRF originated. Each independent evaluator was in charge of determining whether a T2T approach was indeed implemented for any individual patient. Discussions were held among the two committee members in equivocal cases until a consensus regarding T2T implementation was reached. According to the study guidelines, the T2T approach was said to be implemented for any patient if all the following 3 criteria were present in at least 3 out of 4 clinic visits: (1) a validated disease activity score was recorded by the treating clinician during each clinic visit, (2) appropriate treatment changes corresponding to the disease activity score were recommended in the clinic visit note, (3) where appropriate, any deviation from making such a change in RA management was explained by the treating physician (i.e., presence of medication side effects, hospitalizations, infections, pregnancy, patient preference, etc.).

Statistical Analysis

Demographic and clinical characteristics were presented using a descriptive analysis. The associations between T2T implementation and categorical and continuous variables were assessed using the Chi square test, t-test, or Mann–Whitney test. ANOVA or the Kruskal–Wallis test was used to compare continuous variables between centers. All data were analyzed using the Statistical Package for Social Sciences (SPSS®), version 21 (IBM Corp.; Armonk, NY, USA) software. All tests were 2-sided and $p<0.05$ were considered statistically significant.

Results

Study population characteristics

The study included 724 RA patients with a mean age of 62.6±13.0 years and 575 (80.4%) women. The lag time was about a year from the time of onset of disease symptoms until RA diagnosis and the mean RA disease duration was 10.8 years (Table 1). The ethnic background of the patients was representative of the national census bureau statistics in the year the study was conducted, with 533 (78.5%) Jewish and 128 (18.9%) Arab patients. The majority of the patients were of urban representation (86.8%), non-smokers (84.1%), and non-alcohol users (82.7%). Most of the patients (72.4%) had comorbidities, particularly hypertension (45.3%), hyperlipidemia (37.7%), and osteoarthritis (23.7%). Most patients were seropositive for RF and positive for erosive disease, although only a small percentage of patients were on work disability status (4%). The majority of patients had a history of synthetic DMARD or combination of synthetic and biologic DMARD therapy, with low-to-moderate disease activity, except RAPID-3 scores that showed high disease activity in the only one medical center (interestingly, CDAI scores also recorded for this patient population in this particular medical center corresponded to a low-to-moderate disease activity as in the other medical centers; data on file).

DAS and T2T implementation

DAS-28 was used to track disease activity in 46.7% of the patients, followed by CDAI (34.3%), RAPID-3 (12.6%), and SDAI (8.1%). In 38.1% of patients, more than one disease activity measure was used to track disease activity (Table 2). Overall, there was a wide variability in T2T implementation for the management of RA patients among the various centers. The rate of implementation ranged from 11.1% to 87%, with an average of 33.8%. Parameters affecting T2T implementation included age and RF positivity; T2T adherence was higher in younger RF-positive patients with an average disease duration of 10.8 years (Table 3). Other factors, such as sex, ethnicity, education, marital sta-

Table 1. Study population characteristics

Parameter		Number (N) (%)	p**
Demographic data			
Age, years	Symptoms onset	50.6±15.6	NS
	Diagnosis	51.5±15.5	NS
Sex	Male	140 (19.6%)	NS
	Female	575 (80.4%)	
Ethnicity	Jewish	533 (679) (78.5%)	<0.0001
	Arabs	128 (679) (18.9%)	
	Other	18 (679) (2.7%)	
Education (graduation)	≤12 years	227 (418) (54.3%)	NS
	>12 years	191 (418) (45.7%)	
Marital status	Single	44 (647) (6.8%)	NS
	Married	474 (647 (73.3%)	
	Widowed	80 (647) (12.4%)	
	Divorced	49 (647) (7.6%)	
Place of residence	Urban	592 (682) (86.8%)	<0.0001
	Rural	90 (682) (13.2%)	
Employment	Employed	191 (512) (37.3%)	<0.0001
	Not employed	280 (512) (54.7%)	
	Disabled	41 (512) (4%)	
Smoking	Current	86 (540) (15.9%)	<0.0001
	Past	101 (18.7%)	
	Never	353 (540) (65.4%)	
Alcohol use	Never	407 (492) (82.7%)	<0.0001
	Ever	85 (492) (17.3%)	
Comorbidities		524 (724) (72.4%)	<0.0001
Hypertension		296 (653) (45.3%)	<0.0001
Diabetes mellitus		125 (651) (19.2%)	NS
Hyperlipidemia		245 (650) (37.7%)	NS
Ischemic heart disease		52 (647) (8%)	NS
Congestive heart failure		14 (645) (2.2%)	NS
Chronic renal failure		11 (648) (1.7%)	NS
COPD		29 (647) (4.5%)	0.007
Asthma		27 (646) (4.2%)	NS
Malignancy	Past	55 (646) (8.5%)	NS
	Present	9 (646) (1.4%)	0.014
Thyroid disease		109 (647) (16.8%)	0.01
Chronic liver disease		20 (645) (3.1%)	NS

tus, place of residence, employment, smoking status, and the presence of co-morbidities did not influence T2T implementation. Interestingly, the presence of anti-CCP positivity, bone erosions, and medication use (conventional versus biologic DMARDs) did not affect T2T implementation as well (Table 3).

Discussion

The T2T concept has gained much attention in the care of RA patients since the recommendations were published in 2010. While data are still being collected on the relative efficacy of the T2T approach in promoting lower RA disease activity, a recent large, systematic review of clinical trials assessing the clinical and cost-effectiveness of T2T strategy in RA (19) concluded that there is value in pursuing T2T strategy specifically in early RA patients due to higher remission rate achieved in this patient population treated using this strategy. There was no clear evidence with respect to following any particular disease activity target as being more or less effective or safe compared to any other disease activity target, as long as a disease activity target was indeed being followed in the disease management (19) Furthermore, studies incorporating real-life data, such as from the 2-year PEARL study conducted in a hospital-based clinic setting, have shown that a significant increase in the treatment intensity was associated with a significantly higher percentage of patients in remission and reduced progression of the erosion component of the Sharp van der Heijde score (20). Based on this information, we aimed to evaluate the real-life implementation of the T2T approach in daily clinical practice relevant to RA management.

In Israel, the Israeli Rheumatology Association (IRA) initiated T2T implementation by convening an advisory board in October 2011 and witnessed an active participation of 11 rheumatology division chiefs across Israel. Preceding this board, a T2T survey was conducted in September 2011 to evaluate the level of agreement to the T2T concept and gaps in T2T implementation among 127 Israeli rheumatologists; 107 (84%) of rheumatologists participated in the survey, with an average acceptance rate of 65% for the T2T recommendations (data on file). To assess T2T implementation in the real-world clinical practice, our study was designed to choose charts prospectively over a month from routine clinic visits to decrease selection bias. We showed that T2T implementation in the actual clinical practice is limited to about one-third of the Israeli RA patients across the country. While this rate of T2T implementation is lower than that reported in Canada, wherein a recent survey of patients on the physician

Table 1. Study population characteristics (continue)

Parameter		Number (N) (%)	p**
Demographic data			
Osteoarthritis		154 (649) (23.7%)	<0.0001
Fibromyalgia		47 (647) (7.3%)	0.002
Disease characteristics			
RF positive		399 (601) (66.4%)	
Anti-CCP positive^		174/257 (67.7%)	
Bone erosion		125 (209) (59.8%)	
Medications	c-DMARDS#	355 (49%)	NS
	b-DMARDS$	89 (12.3%)	
	c-DMARDS and b-DMARDS	263 (36.3%)	
	No DMARDS	17 (2.3%)	

**p value among the 7 participating centers
^Anti-CCP status was only available for 257 patients out of 724 because anti-CCP positivity was covered by the national healthcare plan in 2012
#azathioprine, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, minocycline, or sulfasalazine
$abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, or tofacitinib
c-DMARDS: conventional disease-modifying anti-rheumatic drugs; b-DMARDS: biological disease-modifying anti-rheumatic drugs; CCP: cyclic citrullinated protein; COPD: chronic obstructive pulmonary disease; N: number of patients; NS: non-significant; RF: rheumatoid factor

Table 2. Disease activity scores and T2T implementation

Visit characteristics		p	p*
Number of visits with disease activity score	>2	276 (38.1%)	<0.0001
Score used	DAS-28	260 (46.7%)	
	SDAI	47 (8.1%)	
	CDAI	198 (34.3%)	
	RAPID-3	73 (12.6%)	
Average score**	DAS-28	2.5 (0.8-29.2)	
	SDAI	8 (0-56)	
	CDAI	10.2 (0-68)	
	RAPID-3	13.3 (0-27.3)	
T2T implementation	Yes	245 (33.8%)	<0.0001

*p value among the 7 participating centers
**median (range)
DAS: disease activity score; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index; RAPID-3: Routine Assessment of Patient Index Data; T2T: treat-to-target

implementation of T2T approach showed 86% adherence to recommendations on the frequency of adjustment of drug therapy and 95% adherence to maintenance of treatment targets by treating physicians, (21) and Malaysia, wherein the T2T implementation was carried out in the management of 81.7% of RA patients (22), it was higher than that recorded in the TRACTION trial on T2T implementation in 11 US-based academic rheumatology centers (where T2T adherence ranged as 11–33.1% depending on the academic center) (23) as well as in Australia, wherein only measures, such as erythrocyte sedimentation rate, hemoglobin level, and C-reactive protein, were used most often for following disease activity (>80%). DAS28 was very infrequently recorded (16.3%) (24) Similar to these studies, the majority of our participating rheumatologists came from academic medical centers, which is representative of the rheumatology practice in Israel, and 80% of the Israeli rheumatologists work in rheumatology clinics affiliated to academic medical centers. Similar to Malaysia, DAS28 and CDAI were the most frequently used disease activity measures (22) unlike the US where the Health Assessment Questionnaire (HAQ) and its variants, such as RAPID-3, are most frequently used followed by CDAI (25). Importantly, our data corroborate previous reports from other countries regarding the relative lack of adherence to the implementation of T2T strategy in RA management and extends these findings to further show the relative lack of T2T implementation in routine clinical practice based on the data collected from actual patient chart notes and not merely from physician or patient surveys as previously done in most studies from other countries. Taken together with the results of previous studies from other countries, our study highlights that the lack of adherence to the T2T approach is a universal issue across rheumatology practices worldwide.

A recent study based on an online survey of 439 American rheumatologists examining the adherence to the T2T strategy and barriers to its implementation in clinical practice stated that one of the reasons for non-adherence to the T2T treatment strategy in the US was related to logistics (i.e., time constraints [62.5%] and lack of efficiency in reporting metrics in the electronic medical records [34.8%]) (25). In contrast, the hindrances for T2T implementation mentioned in the Malaysian study were the inability to escalate DMARDs due to side effects (18.8%), lack of funding for biologic DMARDs (15.6%), and persistent disease despite optimal treatment (14.1%) (22). In Israel, the IRA survey from September 2011 showed that the barriers to the implementation of the T2T approach primarily centered on time constraints in daily practice (73%) and the potential lack of support by the national healthcare plan (25%) (data on file).

In our study, RA patients mostly had well-controlled disease on medical therapy, which may have impacted the adherence to T2T strategy, particularly in patients with long-standing, stable disease. Of note, while T2T recommendations discuss the importance of considering patient comorbidities and preferences in the T2T strategy, our data did not show that these factors affected the adherence to the T2T approach, although our data suggests that >70% of patients had comorbidities. Moreover, in our RA cohort, poor prognostic factors, such as the presence of anti-CCP positivity or erosive dis-

Table 3. Parameters affecting T2T implementation

Parameter		T2T implemented	T2T not implemented	p
Age, years	Symptoms onset	48.6±15.2	51.8±15.7	0.03
	Diagnosis	49.2±15.3	52.7±15.4	0.007
Sex	Male	44 (31.4%)	96 (68.6%)	NS
	Female	201 (35%)	374 (65.0%)	
Ethnicity	Jewish	169 (31.7%)	364 (68.3%)	0.05
	Non-Jewish	59 (40.4%)	87 (59.6%)	
Education (graduation)	≤12 years	111 (48.9%)	116 (51.1%)	NS
	>12 years	92 (48.2%)	99 (51.8%)	
Marital status	Married	176 (37.1%)	122 (70.5%)	NS
	Not married	51 (29.5%)	298 (62.9%)	
Place of residence	Urban	201 (34%)	56 (62.2%)	NS
	Non-urban	34 (37.8%)	391 (66.0%)	
Employment	Employed	83 (43.4%)	108 (56.5%)	NS
	Unemployed	115 (41.0%)	165 (58.9%)	
	Disabled	16 (39.0%)	25 (60.9%)	
Smoking	Current	28 (32.6%)	58 (67.4%)	NS
	Past	37 (36.6%)	64 (63.4%)	
	Never	151 (42.8%)	202 (57.2%)	
Alcohol use	Never	167 (41%)	240 (59.0%)	0.009
	Ever	48 (56.5%)	37 (43.5%)	
Comorbidities	Present	182 (34.7%)	342 (65.3%)	NS
RF positive	Positive	161 (40.4%)	238 (59.6%)	0.01
Anti-CCP positive	Positive	54 (31.0%)	120 (69.0%)	0.809
Bone erosions	Present	70 (56.4)	55 (44.0%)	NS
Medications	c-DMARDS[#]	118 (33.2%)	237 (66.7%)	
	b-DMARDS[$]	33 (37.1%)	56 (62.9%)	
	c-DMARDS and b-DMARDS	90 (34.2%)	173 (65.8%)	NS
	No DMARDS	4 (23.5%)	13 (76.5%)	
	Steroids	106 (32.5%)	220 (67.5%)	NS

[#]azathioprine, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, minocycline, or sulfasalazine
[$]abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, or tofacitinib
c-DMARDS: conventional disease-modifying anti-rheumatic drugs; b-DMARDS: biological disease-modifying anti-rheumatic drugs; CCP: cyclic citrullinated protein; NS: non-significant; RF:rheumatoid factor

ease, did not influence the adherence to the T2T strategy. Our data are in line with those of the Canadian Early Arthritis Cohort, which showed that the presence or absence of anti-CCP measurement did not impact treatment intensification decisions in these patients (26). However, unlike our study, it was a physician global assessment and not objective disease activity measures, such as DAS-28, that was associated more often with the intensification of treatment regimen in early RA patients in Canada (27). In Israel, HAQ-based scoring systems, such as RAPID-3, have not gained great popularity, probably because of their reliance on subjective measures rather than the joint counts that are more objective. It is of interest that in the single medical center where RAPID3 and CDAI scores were both recorded for each patient, these two scores did not correlate well with each another; RAPID-3 scores indicated to more severe disease activity than the corresponding CDAI scores. This contradicts recent data showing good correspondence between RAPID-3 and CDAI scores (28) and such variations may exist because of the subjective nature of this scoring system and may explain its relative lack of popularity in Israel.

The strengths of our study were in the relatively large number of geographically distributed patients. In addition, our study design was chosen to minimize biases in selecting patient charts to examine the actual day-to-day adherence to T2T implementation and did not estimate the adherence based on self-reported practices as would be the case of surveys. The limitation of our study was the lack of data collection on the identity of the rheumatologists whose patients were included in the study; therefore, we cannot assess whether any clinician-related factors, such as years in practice, could have affected the adherence to the T2T strategy. Moreover, our study did not focus on elucidating the reasons behind the low rate of T2T implementation, although we could to gather some data on this topic from the IRA survey from September 2011, as previously described.

The future aims of our research are to study the relation between the lack of T2T approach in RA management and RA disease control. We also intend to work on establishing a learning collaboration for the implementation of T2T in RA rheumatology practices. Notably, this approach was recently implemented successfully in the TRACTION trial, where T2T adherence improved from 13% at the various test sites in the US to 58%, with a sustained adherence of 52% at the end of the intervention phase of the study (29).

Our results show that the implementation of T2T approach in daily practice is carried out in the management of only about one-third of RA patients across Israel. The rate of implementation was higher in younger RF-positive patients. Taken together with similar findings from previous studies of low rates of T2T implementation across various countries, the findings of the present study highlight the universal problem in RA management. Future studies should investigate the reasons for the lack of adherence to the T2T approach among

rheumatologists. In addition, the impact of lack of T2T implementation on RA disease activity and progression should be explored, and intervention strategies aiming to increase T2T adherence should be implemented.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Carmel Medical Center Haifa Israel (CMC0047).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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