Reumatología Clínica

Original Article

Adjustment in the Clinical Practice of *Treat-To-Target* Guidelines for Rheumatoid Arthritis: Results of the ToARCan Study ☆

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A B S T R A C T

Objective: To analyze compliance with T2T clinical practice guidelines.
Methods: Cross-sectional observational study in consecutive patients with rheumatoid arthritis (RA) in 5 hospitals in the Canary Islands. Patients filled out activity scales, HAQ and answered the question of whether the doctor had explained the treatment target. The rheumatologist also collected: visits in the past year, use of activity indices and HAQ, DAS28 of current visit and date of the next visit. The percentage of compliance to indicators based on the T2T recommendations (R) 1, 3, 5–7 and 10 was analyzed.
Results: A total of 343 patients were recruited, 77% female, mean age 57, RA duration of 10 years. Median visits in the last year were 3 and mean time between last and current visit was 5.6 months. A total of 93% of the patients were treated with DMARDs and 44% were in remission by DAS (R1). In the previous visit, documented joint count was present in 85%, a HAQ in 19%, patient VAS in 41%, and a DAS28 in 35% of the patients (R6). The next visit was scheduled at an average of 4.3 months (R5). In 64% of patients with DAS28> 3.2 a visit between one and 3 months was scheduled (R5). A total of 96% of patients said they had been informed of the treatment target (R10). Variability between centers existed but was moderate. The only factor determining the performance of a DAS28 in the last visit was the patient's center of origin.
Conclusions: The Canary Island centers studied achieved high levels of remission and low activity in their patients. The performance of composite indices and follow-up frequency recommended by the T2T are met, although there is room for improvement.

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Ajuste en la práctica clínica de las directrices *treat-to-target* para la artritis reumatoide: resultados del estudio ToARCan

R E S U M E N

Objetivo: Analizar el cumplimiento de las directrices t2t en la práctica clínica.
Métodos: Estudio observacional transversal en pacientes consecutivos con artritis reumatoide (AR) de 5 hospitales canarios. Los pacientes cumplimentaron escalas de actividad, el HAQ y respondieron si el médico les había explicado el objetivo del tratamiento. El médico recogió además: visitas en el último año, empleo de índices y HAQ, DAS28 de la visita actual y fecha de la siguiente consulta. Se analizó el porcentaje de cumplimiento de las recomendaciones t2t (R) 1, 3, 5–7 y 10.

Resultados: Se reclutó a 343 pacientes, 77% mujeres, con edad promedio de 57 años y duración de la AR de 10 años. La mediana de visitas en el último año fue de 3 y el promedio de meses entre la visita anterior y la actual de 5,6. El 93% estaba en tratamiento con FAME y el 44% en remisión por DAS (R1). Se había realizado recuento articular en la visita previa al 85%, HAQ al 19%, EVA actividad del paciente al 41% y DAS28 al 35% (R6). La siguiente visita se programó en un promedio entre uno y 3 meses (R5) al 64% de los pacientes con DAS28 > 3,2. El 96% de los pacientes dijo haber sido informado del objetivo del tratamiento (R10). La variabilidad entre centros era moderada, pero existía. El único factor que determinaba la realización de un DAS28 en la última consulta era el centro de procedencia del paciente.
Conclusiones: Los centros canarios estudiados logran altas cotas de remisión y baja actividad en sus pacientes; la realización de índices compuestos y la frecuencia de seguimiento recomendado por el t2t se cumplen, aunque hay oportunidad de mejora.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease that causes pain and progressive deterioration of the functional capacity of the patients if not properly treated. In recent years, in addition to new therapies for the treatment of this disease, it has been shown that early diagnosis, together with close follow-up of the patients, achieves higher rates of remission or low disease activity.[1–3]

The treat-to-target, or T2T, strategy, which could be defined as aiming for treatment goals, is an ambitious initiative promoted, after reaching a consensus, by the rheumatology community on an international level.[4] It is based on treating RA patients to reach a specific therapeutic goal, which ideally is considered to be clinical remission or, failing that, maintenance of the disease at the lowest possible activity level. Moreover, it recommends seeing patients frequently to reach the goal, using activity scores and quantifying the functional capacity and structural damage. Since the publication of the T2T recommendations in 2010,[4] there has been little information on how they are being implemented in rheumatology departments,[5,6] and some professionals maintain that their implantation is not simple.[7,8] However, knowing that it is a strategy with confirmed results,[2,3,9,10] our goal as a community would be to apply it fully. Knowing how RA patients are being followed in real-world practice should serve as an audit to aid in detecting the shortcomings and as a basis for the discussion of how to apply T2T efficiently in rheumatology. The ultimate goal would be to be able to offer close monitoring of the disease to all the patients in order to improve their quality of life and prevent disability over the long term.

The aim of our study was to analyze the application of T2T in a multicenter study in the Canary Islands, and describe compliance according to the characteristics of the patients, for example, whether their disease was of recent onset or whether they had been treated with biological agents.

Methods

The ToARCan study was a cross-sectional observational study carried out in 5 hospitals in the Canary Islands between March 2013 and March 2014.

Patients

Consecutive patients being treated in the rheumatology outpatient clinic of the participating centers. The patients had to meet the criteria for RA (American College of Rheumatology, 1987 or 2010) and be over 18 years of age; they could be of either sex. Those from whom it was not possible to obtain a reliable questionnaires due to a language barrier and patients who had been in rheumatology follow-up for less than 6 months were excluded.

The study was approved by the clinical research ethics committee of Hospital Universitaria de Gran Canaria Dr. Negrín, Gran Canaria, Spain, and the patients provided their signed consent.

Measurements and Data Collection

All the data were collected during a single visit. The patients were asked to provide their personal medical data and to fill out a patient questionnaire. They completed the pain scale and disease activity data, as well as the Health Assessment Questionnaire (HAQ), and responded to a question as to whether their physicians had explained the goals that they were going to try to achieve with the RA treatment. The physicians collected the following data from the patients' medical records: patient age, sex, time since onset of the disease, rheumatoid factor, anti-cyclic citrullinated peptide (CCP) antibodies, extra-articular manifestations, tobacco use, previous treatments, visits over the last year in which activity scores were collected (physician and patient scores, tender joint count [TJC], swollen joint count [SJC], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], disease activity score [DAS], simplified disease activity index [SDAI], and HAQ), and radiographies of hands and feet that had been carried out over the preceding 5 years. In that visit, the following data were collected for the study: measures necessary for calculating the DAS28, active treatments (including glucocorticoids, disease-modifying antirheumatic drugs [DMARD] and biological agents) and approximate date of the next visit.

The study outcome measures were compliance with the T2T recommendations, some of which were adapted for the study as indicators, as specified in Table 1. The indicators were gathered from data collection forms by the research team, the members of which were blinded to the hospital from which the forms had come.

Statistical Analysis

A descriptive analysis was performed using the group of patients as a whole, then by sex and by hospital, as well as by the duration of RA (<3 years) and whether or not they were being treated with biological agents. The percent compliance with the recommendations in Table 1 was calculated with the 95% confidence interval. To compare the results between groups, the chi-square method was used for categorical variables and analysis of variance for continuous variables. We studied the factors associated with the calculation of the DAS28 in the last visit, as the clearest exponent of compliance with the T2T strategy, using logistic regression where the dependent variable was the utilization of the DAS28 (yes/no) and the variables studied: hospital, patient age and sex, number of DMARD, number of biological agents, RF and anti-CCP antibodies, and duration of the disease. We used the Stata v.11 statistical software package and statistical significance was set at $P<.05$. The

Table 1
Measures of compliance with the treat-to-target (T2T) strategy.

	T2T recommendation	Measure of the compliance in ToARCan	Value (%)
1	The primary goal of RA treatment should be a state of "remission" of the arthritis	Of patients in RA remission according to the DAS28-ESR (<2.6) and SDAI (≤3.3) scores	66
3	A low disease activity can be an acceptable alternative as the therapeutic target in established RA	Of patients with low RA activity according to the DAS28-ESR (<3.2) and SDAI (≤11) scores	83
5	The measure of disease activity should be obtained and documented regularly; every 1–3 months in patients with high or moderate disease activity and every 3–6 months in patients with low disease activity	Of patients with active RA defined by a DAS28-ESR ≥3.2 score, who are scheduled for the next visit within a time interval no longer than 3 months	77
		of RA patients with low RA activity defined by a DAS28-ESR <3.2, who are scheduled for the next visit within a time interval no longer than 6 months	
			51[a]
6	The use of validated scores for measuring disease activity, which includes joint counts, is necessary in routine clinical practice to guide treatment decisions	Of patients in whom, during the previous visit, the performance of TJC, SJC, patient VAS, physician VAS and DAS was documented	93[a]
7	Structural changes and functional and radiologic damage should be taken into account when making clinical decisions, in addition to the activity scores or disease status	Of patients who were given the HAQ questionnaire at some moment within the past year	22[a]
		Of patients who had undergone radiography of hands and feet in the past 5 years	82[a]
10	The patient must be properly informed about the specific treatment goal and the strategy planned to achieve it under the supervision of the rheumatologist	Of patients who responded positively to the question "Has your specialist explained the goal that is expected be reached with the treatment?"	96[a]

DAS28: Disease Activity Score; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count; VAS: Visual Analog Score.

[a] The difference between centers is statistically significant (*P*<.05).

sample was large enough to estimate percentages of compliance with any recommendation lower than 10% and for the multivariate analysis.

Results

In all, 343 patients were included (77% women), with a mean age of 57 years and a mean duration of RA of 10 years. Table 2 shows the characteristics of the patients included.

Table 1 shows the overall results for the indicators based on the T2T recommendations. The percentages of remission and of low disease activity were very high, and there were no statistically significant differences between hospitals. The recommendable times between visits were appropriate for patients with high activity in general, but there were differences between hospitals in terms of the percentage of patients with no activity seen before 6 months had elapsed, which ranged between 34.8% and 77.8%. The frequency of determining activity scores was also very high, although there were differences between centers; nevertheless, the lowest rate of implementation of a scoring system of some type for any center was 78.4% of all the patients. Less common was the performance of some measure of the patients' function, with the rates for the 5 hospitals ranging from 0% to 37.8% (*P*<.001). The majority of the patients had a radiograph of feet or hands from the preceding 5 years, although only 14.6% from the preceding year (*P*=.008 between hospitals) and the patients had been properly informed by their doctors about the treatment goals (range: 77%–100%; *P*<.001).

The median of visits over the preceding year, including the current visit, was 3 (interquartile range [IQR]: 2–4). The average time elapsed between the previous visit and the current visit was 5.5 ± 2.3 months (mean $\pm$ standard deviation [SD]), and was shorter among the patients with a history of RA of 3 years or less (4.9 ± 2.5). Table 3 shows the adaptation broken down by duration of the disease and treatment with biological agents at the present time.

Table 2
Characteristics of the patients included in the ToARCan study (2013–2014).

Characteristics	Value for the sample recruited No.=343	No. of patients
Women, n (%)	266 (77.6)	343
Average age in years, mean (SD)	56.8 (13.0)	342
Mean duration of the disease in years, mean (SD)	10.7 (8.2)	331
Less than 3-year history of arthritis, n (%)	51 (15.4)	331
Erosive arthritis, n (%)	166 (52.0)	319
HAQ score, mean (SD)	0.82 (0.68)	336
Positive rheumatoid factor, n (%)	281 (82.2)	342
Positive anti-CCP antibodies, n (%)	203 (77.3)	277
Extra-articular manifestations,[a] n (%)	34 (10.5)	324
Tobacco use, n (%)		
Smokers	74 (22.9)	338
Ex-smokers	61 (18.0)	
Never smoked	203 (60.0)	
Treatment with DMARD,[b] n (%)	319 (93.0)	337
Treatment with biological therapies,[c] n (%)	101 (30.0)	337
Treatment with corticosteroids, n (%)	161 (47.8)	337
DAS28[d] in the current visit, mean (SD)	2.9 (1.3)	304
Status according to DAS28, n (%)		
<2.6 remission	136 (44.7)	304
<3.2 low activity	188 (61.8)	
≥3.2 activity	116 (38.1)	

CCP: cyclic citrullinated peptide; DAS28: Disease Activity Score; DMARD: disease-modifying antirheumatic drugs; HAQ: Health Assessment Questionnaire; SD: standard deviation.

[a] The patient has or has had at some point in the disease course one or more of the following conditions: pulmonary fibrosis, Sjögren's syndrome or rheumatoid nodules.

[b] A total of 38 patients received 2 or 3 DMARD.

[c] 9% in the case of patients with a history of RA of ≤3 years.

[d] Formula with erythrocyte sedimentation rate (ESR).

Table 3
Compliance with time-to-treatment (T2T) recommendations selected according to the duration of the disease and current use of biological therapies.

T2T criteria	Compliance with the recommendations % (95% confidence interval)		
	All the patients (n=343)	History ≤3 years (n=54)	Receiving biological therapy (n=101)
R1: Clinical remission according to DAS28-ESR or SDAI	66 (61–71)	74 (62–87)	57 (48–87)
R3: Low activity according to DAS28-ESR or SDAI	83 (79–87)	94 (87–100)	79 (71–87)
R5: Active RA (DAS28-ESR ≥3.2) scheduled for the next visit within a time interval no longer than 3 months	77 (65–88)	NE	81 (63–99)
R5: Low RA activity (DAS28-ESR <3.2) scheduled for the next visit within a time interval no longer than 6 months	51 (45–57)	63 (48–77)	60 (49–71)

DAS28: Disease Activity Score; ESR: erythrocyte sedimentation rate; NE: not evaluable (only 3 patients met the condition); RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index.

The DAS28 had been calculated during the previous visit in 218 patients (63.6%), 25 (49.0%) of whom had a history of RA of 3 years or less and 68 (67.3%) were receiving biological therapy. The multivariate analysis of the factors that determined the calculation of the DAS28 during the previous visit showed a lack of association with patient-related factors and a clear relationship to the center (in one center, the odds ratio versus the hospital used as a reference for the measurement of the DAS28 was 2.15 and in another, 0.4 [*P*<.05 in both cases]).

Discussion

We evaluated compliance with the recommendations of the T2T strategy in the Canary Islands. In general, we can say that there is a high rate of compliance, even with moderate variability among centers.

Our audit illustrates, in a sample that is clearly representative of RA patients from 5 hospitals, the nature of clinical practice in our region: patients visit the rheumatology departments an average of 3 times a year and, although joint counts are carried out in more than 80% of the patients, the patient scores and the DAS28 are documented in the medical records in less than half. In cases of active RA, two thirds of the patients had their next visit scheduled within the recommended period of 1–3 months.

The T2T philosophy states that the important thing is the strategy, more than the specific agent employed, showing that, with a combination of nonbiologic DMARD, it is possible to achieve the same low activity or remission as with biological therapies in many patients.[3] The analysis of compliance with the T2T recommendations with its valuable feedback should contribute to achieving better control of the disease activity and comorbidities on the part of rheumatologists. Treatment-to-target does not necessarily mean the application of more costly therapy; in fact, it has been reported that close follow-up can be associated with a reduction in the use of biological therapy achieved with a sensible utilization of conventional therapies.[11]

The T2T studies have been shown to offer clear advantages in recent-onset arthritis.[12] Patients with strict control improve more and sooner than those treated with conventional approaches, and the average difference can be up to 1 point in the DAS28. Nevertheless, there is a need for studies to determine whether the strategy has clear advantages in established RA.[13] There is also a lack of cost studies comparing the intensive strategy with the standard approach.[12] In this respect, the lack of support for T2T strategies in established RS is reflected in our study in the variability observed among hospitals when all the patients are taken into account, which is reduced when only the RA patients with the most recent onset of the disease are considered.

Kaneko et al. published a survey of 300 Japanese rheumatologists concerning the obstacles to the implementation of T2T, that showed that, in Japan, the degree of agreement with T2T in general is very high, although there are certain barriers to its application. Among them, it can be seen that only 45% of the professionals employs composite scores, only 44% monitor their patients with radiological techniques and only 14% with the HAQ. In addition, Japanese rheumatologists only discuss the treatment with the patients in 56% of the cases, and half of those who do not hold this discussion justify it by explaining that the patients are not fit or cannot make decisions. In Italy, Caporali et al. surveyed 100 rheumatologists to measure the degree of acceptance and applicability of the T2T criteria.[14] They observed that agreement with the recommendations is high; however, it is difficult to maintain the treatment target throughout patient follow-up or the course of the disease. Haraoui et al. carried out a similar survey in Canada and revealed that the level of agreement was not high (6.92 of 10) concerning the frequency with which activity scores should be calculated (recommendation 5) or in the use of composite scores. However, the level of agreement for the rest of the recommendations is high.[15] In our study, based on patient data, the actions of the rheumatologists show that, in general, acceptance is high, except, perhaps, with respect to the frequency of visits and measurements, despite the fact that an increase in the latter has been shown to improve the outcome and change therapeutic decisions.[16] However, reluctance still exists, especially because of the belief that they prolong the consultation time.

A number of published studies have dealt with the barriers to patient access to T2T. Patients with moderate disease activity may not want intensive treatment because they are satisfied, despite the fact that two thirds of the satisfied patients had moderate or high activity.[17] This shows that the degree of disease activity in RA is sometimes assessed in different ways by physicians and patients, a circumstance that is demonstrated, at least with regard to pain and joint counts.[18] Patients may assume that the improvement they have experienced is relevant and not be convinced that a change could result in greater benefits, in addition to the inconvenience of frequent visits and the fear of adverse drug effects. The paradox is that, if the patient is informed of the goal, as the guidelines clearly recommend, the target values of the T2T strategy may not fare too well. De Wit et al.[19] have published a version of these recommendations that patients can understand, so that, when appropriate, it can be used during visits reduce the discrepancies.

Other barriers to the application of 100% of the T2T strategy can arise from other patient characteristics. For example, there is a proportion of RA patients who do not received DMARD, in our case, nearly 10%. There are several causes for this, such as mild disease, comorbidity or toxicity. In other cases, there may not be access to a rheumatologist or access may be difficult, a circumstance that could also have an impact on the number of visits that can be scheduled. It is necessary to understand that the frequent visits and evaluations in the T2T approach require an infrastructure that sometimes is out of reach for overcrowded care settings. It is obvious that each department or service should adapt the T2T recommendations in order to be able to implement them, including a rheumatology nurse, informative T2T material adapted for patients

and a protocol for RA follow-up, among other options. On the other hand, in some settings, access to all the available pharmaceuticals in a sudden T2T escalation is limited by the administrations or through some form of copayment.

In conclusion, RA patients in the Canary Islands have high rates of remission and low disease activity, and the T2T recommendation are followed in a generalized, but variable, manner. The recommendations that are followed the least are those referring to the use of the scoring systems and the frequency of visits. It is important that we make an effort to adapt clinical practice to the knowledge and to the circumstance, following criteria based on equity.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of Interest

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Acknowledgments

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