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BRIEF REPORT

Treating psoriatic arthritis to target: discordance between physicians and patients' assessment, non-adherence, and restricted access to drugs precluded therapy escalation in a real-world cohort

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Abstract

The treat-to-target strategy (T2T) was associated with better outcomes in psoriatic arthritis (PsA) compared to standard care in clinical trials. This study aimed to analyze factors precluding treatment optimization in a T2T strategy conducted in a real-world cohort of PsA patients. A retrospective cross-sectional study nested in a cohort was conducted. Medical records of patients ≥ 18 years old, fulfilling CASPAR criteria and with at least one visit in the PsA clinic, were reviewed. Demographic data, current medication, and minimal disease activity (MDA) criteria were recorded. Reasons for the non-escalation of therapy in patients who were not classified as MDA were reported as absolute and relative frequencies. In the 8-month period, 131 visits (corresponding to 74 patients) were conducted. The MDA criteria were available in 113 visits (86.3%) and patients were classified as MDA in 31.0% of the visits ($N = 35/113$). Although in 69.0% of the visits patients were not in MDA, ($N = 78/113$), therapy was adjusted in only 42.3% ($N = 33/78$). Reasons precluding treatment escalation in non-MDA subjects were physician's impression of remission (57.7%, $N = 26$), non-adherence to previous prescription (17.8%, $N = 8$), restricted access to drugs (17.8%, $N = 8$), adverse events (11.1%, $N = 5$), poor understanding of medication instructions (6.7%, $N = 3$), patient's refusal to escalate therapy (4.4%, $N = 2$), and recent change in therapy (2.2%, $N = 1$). Discordance between the physician's clinical evaluation and the MDA

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criteria, non-adherence to prescription, and poor access to drugs were the main factors precluding escalation of therapy in a T2T strategy in a real-world PsA cohort.

Keywords Adherence · Minimal disease activity · Psoriatic arthritis · Treatment · Treat-to-target

Introduction

In psoriatic arthritis (PsA), the treat-to-target (T2T) approach requires that anti-rheumatic therapy be chosen and adjusted in such a manner that the suggested goal (clinical remission or alternatively minimal/low disease activity) is achieved and maintained [1–4].

In 2009, the first potential target for treatment in PsA providing an absolute measure of disease state and encompassing multiple domains was published. The minimal disease activity criteria (MDA) for PsA require that patients are classified as minimal disease activity when meeting 5 of the 7 following criteria: tender joint count (TJC) ≤ 1, swollen joint count (SJC) ≤ 1, Psoriasis Area Severity Index (PASI) ≤ 1 or body surface area (BSA) ≤3, patient pain visual analog scale (pain VAS) ≤ 15, patient global disease activity visual analog scale (PtGA) ≤ 20, Health Assessment Questionnaire (HAQ) ≤ 0.5, and tender entheseal points ≤ 1 [5].

The TICOPA trial provided direct evidence that the use of early and intensive treatment in PsA, using the MDA status as the target, can lead to significant improvement in joint and skin outcomes compared to standard care; however, the frequency of immunobiologic drug use (and, consequently, the cost of therapy) was higher in the T2T arm, as well as the incidence of serious adverse events [6].

Studies evaluating the T2T strategy in PsA have diverse targets and are mainly clinical trials [7]. The evaluation of this strategy outside the controlled environment of clinical essays is limited. In other rheumatic diseases such as rheumatoid arthritis (RA), the T2T strategy was effective in improving disease activity and physical function in the real life context [8, 9].

We hypothesize that, in daily practice, several factors affect the tight control strategy and limit treatment escalation in patients who have not achieved the goal. This study aimed to analyze barriers for treatment optimization in a T2T strategy conducted in a real-world cohort of PsA patients.

Patients and methods

A retrospective cross-sectional study nested in a cohort was conducted; the cohort of PsA patients was assembled in 2012 in Hospital de Clinicas de Porto Alegre, a tertiary public university hospital. All patients with PsA diagnosed by a rheumatologist and attending the PsA clinic in this hospital have the following data collected in all visits since 2012: TJC, SJC, pain VAS, PtGA, patient fatigue VAS, patient and physician skin disease/psoriasis VAS, Maastricht Ankylosing Spondylitis *Enthesitis* Score (*MASES*), C-reactive protein (mg/L), and Health Assessment Questionnaire (HAQ) [10, 11]. On June 15, 2016, the T2T strategy was initiated in the clinic and the MDA criteria were included in the protocol. In the routine practice, the escalation of therapy in patients who are not in MDA in the PsA clinic follows the European League Against Rheumatism (EULAR) recommendations for the management of PsA [12].

For the present study, electronic medical records of patients attending the PsA clinic during the 8 months following implementation of the T2T strategy (from 15th of June 2016 to 15th of February 2017) were reviewed.

The patients who participated in this study were covered by a public insurance. In Brazil, in the moment that the study was carried out, only conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and anti-tumor necrosis factor (anti-TNF) drugs were available in the public health system. IL-12/23 and IL-17 inhibitors were only available for patients with private insurance or through a legal proceeding.

Patients ≥ 18 years old fulfilling the Classification Criteria for PsA—CASPAR and with at least one visit to the PsA clinic after the implementation of the T2T strategy were included [13]. Those with other subtypes of spondyloarthritis and/or other associated autoimmune systemic inflammatory rheumatic diseases were excluded. Patients with associated fibromyalgia (FM) were not excluded from the study.

Data collection Demographic data (age, gender) and PsA duration since diagnosis were recorded. Data that are systematically collected in every visit of the PsA clinic were extracted from medical records: current medication, the MDA status (achieved or not), the individual items of the MDA criteria, and the reason for the non-escalation of therapy in visits where patients were not in MDA.

Statistical analysis Quantitative variables were described by mean and standard deviation or median and interquartile range. Categorical variables were described by absolute and relative frequencies. To compare current treatment in patients achieving or not MDA, Pearson's chi-square test or Fisher's exact test were applied. SPSS program version 21.0 was used for statistical analysis [14].

Ethical aspects The research project was approved by the Ethics Committee of Hospital de Clinicas de Porto Alegre (number 170228) and followed statements of Human and Animal Right. A term of commitment for the use of data was signed by all the researchers involved in the study.

Results

During the 8-month period following the T2T implementation in the PsA clinic, 131 visits (corresponding to 74 patients) were conducted; information about the MDA status was available in 113 visits (86.3%) corresponding to 69 patients (93.2%). Although all patients have been followed during several years in the clinic, only those visits occurring after the implementation of the T2T strategy were considered in the analysis. The characteristics of the analyzed patients are described in Table 1.

Patients were in MDA in 31.0% of the visits ($N = 35/113$); 36.2% of the patients ($N = 25/69$) were in MDA in at least one visit during the 8 months of follow-up. Although MDA status was not obtained in 69.0% of the visits ($N = 78/113$), therapy was adjusted in only 42.3% of those visits ($N = 33/78$) (Fig. 1). The main reason precluding treatment escalation was a discrepancy between physician's clinical impression and the MDA status, i.e., physician's clinical impression of PsA remission in spite of a non-MDA result (57.7%, $N = 26$). Other reasons precluding treatment adjustment were non-adherence to previous prescription (17.8%, $N = 8$), restricted access to DMARDs (17.8%, $N = 8$), adverse events (11.1%, $N = 5$), very low educational level and poor understanding of medication instructions (6.7%, $N = 3$), patient's refusal to escalate therapy (4.4%, $N = 2$), and recent change in therapy (2.2%, $N = 1$), i.e., a previous modification in therapy has been implemented up to 3 months and the time to evaluate the efficacy of the previous intervention was still shorter. Five patients (11.1%) had more than one reason to justify the non-escalation of therapy.

The analysis per patient, taking into account only the first visit in which subjects did not achieve MDA, had similar results: 47 subjects (63.5% of the total sample) did not achieve MDA in at least one visit; in those cases, therapy was optimized in only 21 patients (44.7%). Reasons precluding treatment escalation were physician's clinical impression of PsA remission in spite of a non-MDA (57.5%, $N = 19$), non-adherence to previous prescription (12.1%, $N = 4$), restricted access to DMARDs (12.1% $N = 4$), very low educational level and poor understanding of medication instructions (9.1%, $N = 3$), patient's refusal to escalate therapy (6.1%, $N = 2$), and adverse events (3.0%, $N = 1$). Four patients had more than one reason to justify the non-escalation of therapy.

In visits where patients were in MDA ($N = 35$, 31.0%), all patients had ≤ 1 swollen joint and 94.3% had ≤ 1 tender joint, demonstrating that objective/physician reported components of the MDA criteria were commonly fulfilled in this group.

On the other hand, when patients were not in MDA ($N = 78$ visits, 69.0%), the subjective/patient-reported components of the MDA criteria were usually not fulfilled: the pain VAS, PtGA, and HAQ components were not achieved in 96.6%, 95.8%, and 90.0% of those visits, respectively. When rheumatologists reported a clinical impression of PsA remission in spite of a non-MDA result (57.7%, $N = 26$), the objective components of the criteria such as the skin evaluation and the swollen joint count were fulfilled in 84.6% ($N = 22/26$) and 92.3% ($N = 24/26$) of visits, respectively, while the subjective components such as pain VAS and PtGA were fulfilled in only 3.8% ($N = 1/26$) and 0.0% ($N = 0/26$) of those visits, respectively (Table 2).

There was no statistically significant difference in the use of csDMARDs and biological DMARDs (bDMARD) between visits in which patients were in MDA compared with those in which this goal was not reached ($p = 0.979$); in 51.4% ($N = 18/35$) of visits in which patients were in MDA, they were taking only csDMARDs (Fig. 2).

Discussion

This study demonstrated that the T2T strategy in real life, having MDA as a goal, is affected by several factors such as discordance between the physician' s clinical evaluation and the MDA status, non-adherence to prescription, delay to receive drugs from public health insurance, and adverse events of therapy.

Our study demonstrated that it was feasible to perform the MDA criteria in the current practice of a public university hospital since it was available in more than 85% of the visits.

The proportion of patients reaching the goal—MDA status—in our cohort (about 36%) was lower than reported by recent real-world studies, which described 40 to 70.5% of PsA subjects in MDA during the follow-up. However, those studies were registries composed by early PsA patients and cohorts where all the individuals were on biologic therapy [15–17] .

Although the MDA status was proposed as an objective target for PsA treatment in trials and clinical practice, in the present study, the main reason for non-adjustment of therapy in patients not achieving MDA status was the physician's impression that the disease was in remission in spite of the non-MDA status [5]. Rheumatologists were reluctant to escalate therapy when the objective components of MDA score (SJC and PASI/BSA component) were fulfilled. In a previous study, the most common reason for non-MDA in close-to-MDA cases was patient-reported pain (82.4%), followed by PtGA (68.6%) and HAQ (60.8%), demonstrating that

Table 1 Baseline characteristics of the 69 patients included in the analysis

Variables	All patients (N = 69)	Patients who achieved MDA status at least once during the follow-up period (N = 28)	Patients who did not achieve MDA status during the follow-up period (N = 41)	*P* value
Age—mean ± SD	57.4 ± 10.6	57.9 ± 11.1	57.0 ± 10.3	0.744
Female N (%)	37 (53.6)	13 (46.4)	24 (58.5)	0.322
Time since PsA diagnosis (in years)—mean ± SD (range)	12.1 ± 9.7 (0.1–42.2)	10.7 ± 10.3 (0.1–42.4)	13.1 ± 9.3 (0.7–39.6)	0.328
Time since Pso diagnosis (in years)—mean ± SD (range)	17.7 ± 10.6 (0.9–46.4)	17.2 ± 11.9 (0.9–46.4)	18.1 ± 9.8 (2.0–45.0)	0.717
Number of visits per patient*—median (25th–75th)	1 (1–2)	1 (1–2)	1 (1–2)	0.198
Joint involvement				0.209
Oligoarthritis N (%)	19 (27.5)	10 (35.7)	9 (22.0)	
Polyarthritis N (%)	50 (72.5)	18 (64.3)	32 (78.0)	
Patients treated with csDMARDs—N (%)	53 (76.8)	22 (78.6)	31 (75.6)	0.775
Time on current csDMARD in years—mean ± SD (range)	7.3 ± 5.8 (0.1–24.4)	5.2 ± 3.8 (0.6–12.4)	8.7 ± 6.6 (0.1–24.4)	0.031
MTX dose (mg/week)—mean ± SD/N (%) of patients treated with MTX	17.6 ± 4.8/48 (69.6)	17.6 ± 4.6/20 (71.4)	17.5 ± 5.0/28 (68.3)	0.930
Patients treated with bDMARD—N (%)	25 (36.2)	10 (35.7)	15 (36.6)	0.941
Time on current bDMARD in years—mean ± SD (range)	2.0 ± 1.1 (0.2–4.1)	2.0 ± 1.2 (0.4–3.3)	2.1 ± 1.2 (0.2–4.1)	0.826
Patient skin VAS (0–100 mm)—median (25/75 IQR)	16.5 (0.0/50.0)	5.5 (0.0/21.2)	38.5 (0.0/59.0)	0.001
Physician skin VAS (0–100 mm)—median (25/75 IQR)	7.0 (0.0/36.2)	0.5 (0.0/10.0)	21.5 (0.0/70.0)	< 0.0001
Fatigue VAS (0–100 mm)—median (25/75 IQR)	52.0 (11.5/70.0)	13.0 (2.7–50.0)	60.0 (46.2/80.0)	< 0.0001
Pain VAS (0–100 mm)—median (25/75 IQR)	40.0 (15.0/63.5)	14.5 (0.7–36.5)	55.0 (36.0/67.2)	< 0.0001
Patient global disease activity VAS (0–100 mm)—median (25/75 IQR)	39.5 (15.0/59.2)	14.5 (6.0–28.5)	50.0 (35.5/69.2)	< 0.0001
MASES mean ± SD	2.5 ± 4.0	0.3 ± 0.9	3.9 ± 4.6	< 0.0001
Tender joints (out of 68)/mean ± SD	3.5 ± 8.5 (0–64)	0.6 ± 1.1	5.4 ± 10.5	0.006
Swollen joints (out of 66)/mean ± SD	0.8 ± 1.8 (0–11)	0.3 ± 0.6	1.2 ± 2.2	0.013
ESR (mm/h)—mean ± SD	24 ± 21	18.8 ± 14.9	27.9 ± 24.5	0.065
CRP (mg/L)—mean ± SD	7.6 ± 11.9	5.2 ± 6.9	9.3 ± 14.3	0.129
Disability (measures by HAQ) N (%)				
Mild	39 (56.5)	25 (89.3)	14 (34.1)	< 0.0001
Moderate	26 (37.7)	3 (10.7)	23 (56.1)	
Severe	4 (5.8)	0 (0.0)	4 (9.8)	
Patients under dual assessment Dermatologist/rheumatologist N (%)	34 (49.3)	12 (42.9)	22 (53.7)	0.378

SD, standard deviation; *N*, number; *csDMARDs*, conventional synthetic disease-modifying anti-rheumatic drugs; *bDMARD*, biological disease-modifying anti-rheumatic drug; *MTX*, methotrexate; *PsA*, psoriatic arthritis; *Pso*, psoriasis; *VAS*, visual analog scale; *IQR*, interquartile range; *MASES*, Maastricht Ankylosing Spondylitis Enthesitis Score; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *HAQ*, Health Assessment Questionnaire

*Number of visits conducted after the implementation of the treat to target strategy in the clinic and included in the analysis

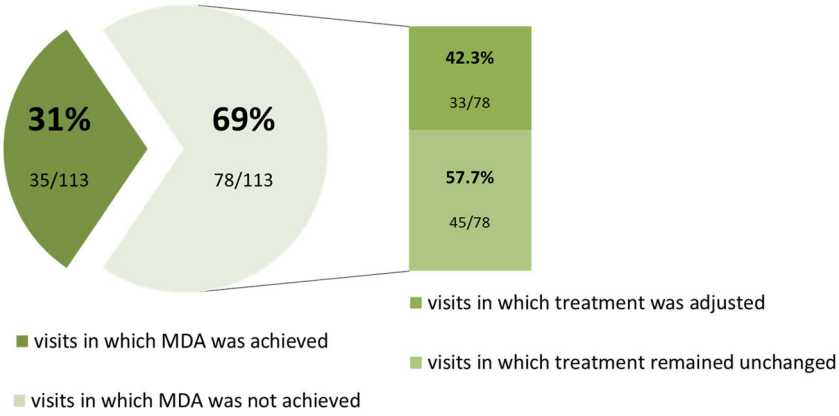

Fig. 1 Evaluation of MDA status in visits and therapeutic decision when patients were not in MDA

Table 2 Individual components of the MDA criteria in visits in which patients were not in MDA status but rheumatologists did not escalate therapy due to clinical impression of remission

Number of visit*	Components of the MDA criteria (*N*/%)**						
	TJC ≤ 1 8 (30.8)	SJC ≤ 1 24 (92.3)	PASI ≤ 1 or BSA ≤ 3 23 (84.6)	Pain VAS ≤ 15 1 (3.8)	Patient global VAS ≤ 20 0 (0.0)	HAQ ≤ 0.5 2 (7.7)	Enthesitis ≤ 1 10 (38.5)
1	X	–	X	X	–	–	–
2	–	–	X	–	–	–	–
3	–	X	X	–	–	–	–
4	–	X	–	–	–	–	X
5	–	X	X	–	–	X	–
6	–	X	X	–	–	–	–
7	X	X	X	–	–	–	–
8	–	X	X	–	–	–	–
9	X	X	X	–	–	–	X
10	X	X	X	–	–	–	–
11	–	X	X	–	–	–	X
12	–	X	–	–	–	–	–
13	–	X	X	–	–	–	–
14	–	X	X	–	–	–	–
15	X	X	–	–	–	–	X
16	–	X	X	–	–	–	–
17	–	X	X	–	–	–	X
18	–	X	X	–	–	–	–
19	–	X	X	–	–	–	X
20	X	X	X	–	–	–	X
21	X	X	X	–	–	–	X
22	X	X	X	–	–	–	–
23	–	X	X	–	–	–	X
24	–	X	–	–	–	X	X
25	–	X	X	–	–	–	–
26	–	X	X	–	–	–	–

MDA, minimal disease activity criteria; *TJC*, tender joint count; *SJC*, swollen joint count; *PASI*, Psoriasis Area Severity Index; *BSA*, body surface area; *VAS*, visual analog scale; *HAQ*, Health Assessment Questionnaire

X: the component was fulfilled

*Visits 6 and 7 are distinct visits from the same patient; visits 8 and 9 evaluate the same patient; and visits 25 and 26 also correspond to the same patient

**Number and perceptual of visits in which the individual component was fulfilled

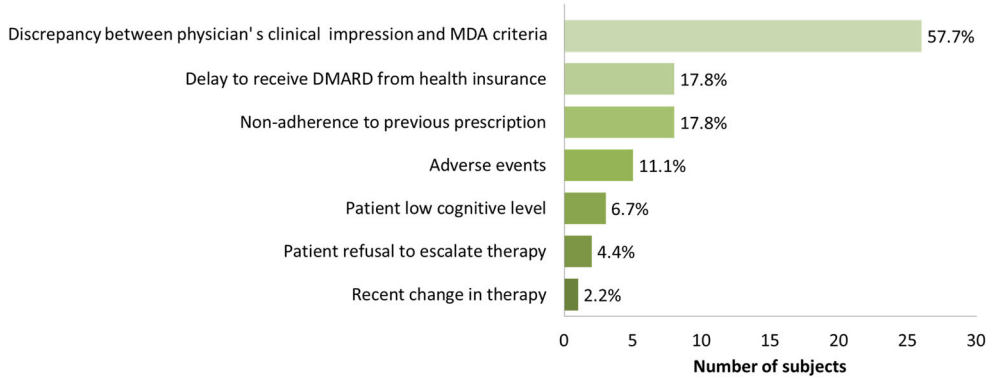

Fig. 2 Reasons for "no escalation of treatment" when patients were not in MDA status

subjective components of the MDA criteria (the PROs) could preclude patients from achieving MDA in cases where the rheumatologist has the clinical impression of remission [16]. In PsA, it has been demonstrated that there is a discrepancy between physicians and patients' assessment of disease, with patients usually scoring their disease worse than physicians [18]. Furthermore, coexisting FM was related to worse disease activity scores and lower prevalence of MDA status in one study (0% of MDA among PsA patients with FM versus 43.3% among PsA subject without FM); the authors highlighted the importance of taking this aspect into consideration in the treatment algorithm to avoid unnecessary upgrading of therapy [19]. The MDA status is suggested to be a tool to guide decision-making in PsA; nevertheless, it could not replace the clinical judgment in the context of an individual patient.

This work also found the modifiable factor "non-adherence to previous prescription" to preclude adjustment of therapy in a real-life T2T strategy. Non-adherence to medication can refer to either (1) poor execution or implementation of the prescribed treatment recommendation leading to omitted or delayed doses and (2) discontinuation of the prescribed treatment [20]. Data on PsA adherence to treatment is still emerging; it has been previously reported that 35.0% of PsA patients discontinue methotrexate in a 2-year period and 50.0% discontinue their first anti-TNF drug in the first year [21, 22]. Among PsA patients receiving etanercept and adalimumab, the percentage of patients with at least a 60-day gap on their medication was high (62–65%) [22]. The inexistence of a "gold standard" for measuring adherence to therapy also limits the research in the field [23].

In this cohort of PsA subjects attending a public hospital in a developing country, another modifiable factor—the restricted access to DMARDs—was the third factor which prevented the upgrade of therapy. At the time of the study, the access to csDMARDs and bDMARDs was limited due to the low educational level of patients and unavailability of drugs in the public health system. The inequities in access to DMARDs across 46 European countries have already been demonstrated in RA; patients living in lower income European countries had less access to csDMARDS and mainly bDMARDs [24]. It is expected that inequities in the access to DMARDs outside Europe would be even larger.

It was suggested that in the TICOPA trial, the tight control strategy was superior to standard care in achieving ACR 20 because more patients in the T2T strategy were exposed to bDMARDS than standard care (36.6 versus 6.7%) [6]. In our real-world study, however, there was no statistical difference regarding the use of bDMARDs between visits in which patients were in MDA or not. Further, in the TICOPA trial, methotrexate monotherapy was used in just over a quarter of the tight control arm with these patients consistently achieving MDA [6]. These data suggests that in a T2T strategy, several patients could achieve the MDA status only taking csDMARDs. In our view, the most important aspect in the management of PsA patients is the strategy of aiming to the achievement of absent or minimal disease activity, irrespective of the drugs used to do so. In our study, the combination of traditional DMARDs, the optimization of their dosage, or route of administration was as effective as the utilization of biologics. The comparison of these drugs might show differences in terms of achieving MDA in a prospective study with long-term follow-up. Moreover, since this is an observational study, patients treated with biological therapy in this cohort were probably the patients with most severe and refractory disease.

Limitations of the study include short time of follow-up and retrospective design. Patients were evaluated during only 8 months since the tight control strategy in PsA was recently initiated in our institution. On the other hand, since preceptors and fellows of the PsA clinic had undergone recent training on the T2T strategy, we were able to find the reasons for not following the strategy in all medical records because physicians justified why they did not adjust therapy when a modification in treatment was expected. A positive point of the retrospective design is that physicians evaluated the patients before the conception of the study and they did not know that they were going to be evaluated in terms of their actions, avoiding some bias on how information was questioned and recorded.

Despite these limitations, we were able to demonstrate factors affecting the T2T strategy in a public hospital in a developing country.

In conclusion, discordance between the physician' s clinical evaluation and the MDA status, non-adherence to prescription, poor access to DMARDs, and adverse events of therapy prevented the adjustment of therapy in a tight control strategy implemented in a real-world cohort of PsA patients.

Changes in modifiable factors such as improvement in patients' adherence and better access to DMARDS could be strategies to optimize the T2T approach in clinical practice.

Compliance with ethical standards

The research project was approved by the Ethics Committee of Hospital de Clinicas de Porto Alegre (number 170228) and followed statements of Human and Animal Right

Disclosure None.

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