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BRIEF REPORT

Daily practice feasibility and effectiveness of treating long-standing rheumatoid arthritis to target with synthetic disease-modifying antirheumatic drugs: a prospective cohort study

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Abstract To prospectively study the daily practice feasibility and effectiveness of treat-to-target (T2T) strategy with synthetic drugs aiming to maintain and achieve disease remission or low activity based on DAS28 and CDAI in long-standing rheumatoid (RA) patients. Two hundred and forty-one consecutive RA patients from Hospital de Clínicas de Porto Alegre were followed for 14 (±5.3)months. At follow-up, patients were evaluated by a rheumatologist at least once every 3 to 4 months. Treatment was adjusted following a step-up strategy, based on the disease activity scores (DAS28 and CDAI), aiming at remission (<2.6 or <2.8, respectively) or at least low disease activity (<3.2 or <10). Patients were predominantly women (84.7 %), mean age 54.9 (±11.9) years with 11.1 (±7.4)years of disease duration. At visit 4, T2T intervention significantly reduced DAS28 (4.6±1.6 vs. 4.0±1.5; $p<0.005$), CDAI [17.8 (8.2–28.7) vs. 12.6 (5.1–22.5); $p<0.001$], and HAQ (1.5±0.9 vs. 1.3±0.8; $p=0.002$). At the end of the study, compared to the baseline scores, more patients achieved remission by DAS28 (11.6 vs. 18.6 %; $p<0.001$) and CDAI (8.1 vs. 13.6 %; $p<0.001$) and also low disease activity by DAS28 (9.8 vs. 13.0 %; $p<0.001$) and CDAI (23.9 vs. 28.4 %; $p<0.001$). Both average doses of sulfasalazine and methotrexate at visit 4 were higher (1375 vs. 1621 mg, $p=0.024$; and 14.5 vs. 16.5 mg, $p<0.001$, respectively). More patients were on combination therapy at the end of the follow-up (48.2 vs. 52.3 %; $p<0.001$). The implementation of T2T strategy in the treatment of RA was feasible and effective in this outpatient population. The optimization of synthetic DMARDs use with dose adjustments and combinations of drugs seemed to improve disease outcome regarding disease activity and functional status.

Keywords Cohort · Effectiveness · Feasibility · Rheumatoid arthritis · Synthetic DMARDs · Treat-to-target

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Introduction

Rheumatoid arthritis (RA) is an autoimmune systemic disease characterized by destructive polyarthritis. Major impacts on RA patients' functional capacity may occur due to persistently active disease. Adjusting disease-modifying antirheumatic drugs (DMARDs) aiming for the lowest disease activity level has been demonstrated to improve RA treatment outcomes in various treat-to-target (T2T) and tight control studies [1–12].

Disease activity tight control strategy prevents joint destruction and disability in RA [13–15].

However, feasibility of the intensive therapy exclusively with synthetic DMARDs still remains to be confirmed. Although strict use of synthetic DMARDs has been proved to be efficacious in clinical trials [3, 7, 11, 16, 17]; real-world data is scant [4, 8, 18]. Since pragmatic studies reflect real clinical scenario better than efficacy trials [19], our objective was to prospectively study the daily practice feasibility and effectiveness of treating RA to target strategy with synthetic DMARDs aiming for remission or low disease activity according to 28-joint disease activity score (DAS28) and clinical disease activity index (CDAI).

Patients and methods

From 2006 through 2007, 241 consecutive adult patients with RA from Hospital de Clínicas de Porto Alegre were followed in the outpatient clinic of the Rheumatology Division. Patients were diagnosed according to the ACR criteria [20] and had established RA. Patients with other systemic inflammatory conditions were excluded. This study was approved by the institutional Ethics Committee, and before inclusion, all patients gave written informed consent according to Declaration of Helsinki.

During follow-up, patients were evaluated by a rheumatologist at least once every 3–4 months. At each visit, clinical

Table 1 Clinical features of patients with RA in baseline and after T2T strategy

	RA patients n=241		p
	Baseline	Visit 4	
Clinical characteristics			
CDAI[a]	17.8 (8.2–28.7)	12.6 (5.1–22.5)	<0.001
DAS28[b]	4.6±1.6	4.0±1.5	<0.005
HAQ[b]	1.5±0.9	1.3±0.8	0.002
Remission by DAS28	11.6	18.6	<0.001
Remission by CDAI	8.1	13.6	<0.001
Low disease activity by DAS28	9.8	13.0	<0.001
Low disease activity by CDAI	23.9	28.4	<0.001
Swollen joint count[a]	4.00 (1.0–8.0)	2.00 (0.0–4.0)	<0.001
Tender joint count[a]	8.00 (2.0–12.0)	3.0 (1.0–9.0)	<0.001
Erythrocyte sedimentation rate[a]	26.0 (14.0–39.0)	23.0 (12.0–40.8)	0.218
Physician's assessment of disease activity[a]	40.0 (18.0–61.0)	30.0 (12.0–56.0)	0.02
Patient's assessment of disease activity[a]	45.0 (23.0–75.0)	38.0 (20.0–62.0)	0.01
Patient's assessment of pain[a]	54.0 (30.0–77.0)	49.0 (28.0–75.0)	0.007
Treatment characteristics			
MTX no. (%)	148 (78.7)	157 (83.5)	0.292
Mean MTX dosage (mg)	14.5	16.5	<0.001
Mean sulfasalazine dosage (mg)	1375	1621	<0.001
Combination therapy	48.2	52.3	<0.001
Concurrent DMARD treatment no. (%)	82 (43.6)	88 (46.8)	0.604
Antimalarial drugs	51 (27.1)	37 (19.7)	0.113
Sulfasalazine	9 (4.8)	7 (3.7)	0.799
Triple therapy	17 (9.0)	22 (11.7)	0.499
Leflunomide	5 (2.7)	22 (11.7)	<0.001
MTX monotherapy, no. (%)	66 (35.1)	69 (36.7)	0.830
Other DMARDs monotherapy, no. (%)	34 (18.1)	24 (12.7)	0.198
No DMARDs, no. (%)	6 (3.2)	7 (3.7)	1.000
Low-dose corticosteroid treatment, no. (%)	113 (60.1)	118 (72.7)	0.672
Corticosteroid dose (mg)	4.8	5.6	0.57

¶Data are presented as number (percentage) of patients

*p<0.05

[a] Values are presented as median, percentiles 25 and 75

[b] Values are presented as mean and standard deviation

assessments comprised 28-joint counts of swollen and tender joints (SJC and TJC, respectively), pain visual analog scale (VAS), evaluator and patient global assessments (EGA, PGA, respectively) by VAS, health assessment questionnaire disability index (HAQ) [21], morning stiffness (MST), and routine blood tests, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The patient's disease activity was quantified by performing DAS28 and CDAI [22].

The therapy of all patients was prescribed strictly according to a step-up strategy based on the use of synthetic DMARDs. Since this was a daily practice study, factors such as the presence of comorbidities, child's wish, and patients' preferences had to be taken into account during treatment choice. Treatment was adjusted if desirable and feasible based on DAS28 and CDAI, aiming for remission (<2.6 and <2.8, respectively) or at least low disease activity (<3.2 and <10, respectively) [23, 24]. At every visit, adverse events, DMARD changes, or dosage modifications due to side effects or lack of efficacy and the use of steroids were registered. Some of the patients with severe disease or persistently high DAS28 and CDAI (>5.1 and >22, respectively) were allocated to use anti-TNF alpha as a separate protocol study. At the end of the study, in order to evaluate treatment effectiveness, all drugs under use and disease activity status were recorded.

The statistical analysis was performed with SPSS 20. Chi-squared tests were used for comparison of dichotomous variables and paired Student's *t* test or Wilcoxon's test was used for continuous variables, depending on data distribution. Correlations between DAS28, CDAI, and HAQ were calculated by Spearman's and Pearson's correlation coefficients. The agreement between disease activity categories by both scores was calculated by kappa statistics.

Results

Patients were predominantly women (84.7 %) of mean (±SD) age 54.9 (±11.9)years old with 11.1 (±7.4)years of disease duration. After 14.3 (±5.6)months, at visit 4, T2T intervention significantly reduced DAS28 (mean±SD) (4.6±1.6 vs. 4.0±1.5; $p<0.005$), CDAI [median (IQR)] [17.8 (8.2–28.7) vs. 12.6 (5.1–22.5); $p<0.001$], and HAQ (1.5±0.9 vs. 1.3±0.8; $p=0.002$) (Table 1). There was a statistically significant decrease in the number of swollen and tender joints, patient's global disease, and pain visual analog scales (VAS) ($p<0.05$). There were no significant changes in physician's VAS and erythrocyte sedimentation rates during follow-up. Compared to the baseline scores, more patients at the end of the study achieved remission by DAS28 (11.6 vs. 18.6 %; $p<0.001$) and CDAI (8.1 vs. 13.6 %; $p<0.001$) and also low disease activity by DAS28 (9.8 vs. 13.0 %; $p<0.001$) and CDAI (23.9 vs. 28.4 %; $p<0.001$) (Fig. 1).

The minimal clinically important difference (MCID) [22] for HAQ (0.22) was achieved in 27.1 % of patients at visit 4, for DAS28 (1.2) in 28.3 % and for CDAI (8.05) in 35 %.

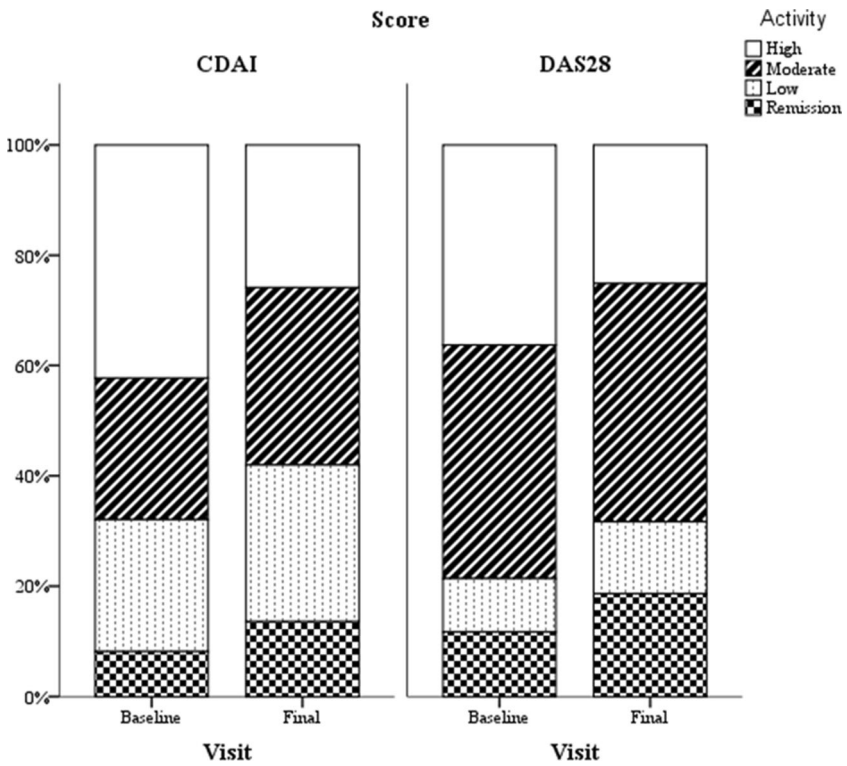

Fig. 1 Disease activity level distribution at baseline and at the end of the study according to CDAI and DAS28

Both average doses of sulfasalazine and methotrexate at visit 4 were higher (1.375 vs. 1.621 mg, $p=0.024$; and 14.5 vs. 16.5 mg, $p<0.001$, respectively). More patients were on combination therapy at the end of the follow-up (48.2 vs. 52.3 %; $p<0.001$). There were no significant changes in average prednisone doses (4.8 vs. 5.6 mg; $p=0.57$).

Discussion

Treating RA with synthetic DMARDs to a target of remission or low disease activity is effective and feasible in daily practice. In our long-standing RA cohort, patients improved their disease activity level and functional capacity with intensive synthetic DMARDs adjustment.

The proportion of patients reaching remission in our study was similar to a cross-sectional single-center [18] and a multicenter [25] real-world studies but smaller than treat-to-target clinical trials [12], probably because our treatment goal included low disease activity. Remission is the primary outcome in most early RA trials; however, low disease activity may be acceptable in some particular clinical scenarios, mainly in long-standing disease and in patients with concomitant fibromyalgia. Alternatively, imaging remission could be a target for these patients as suggested by ultrasound studies [26, 27].

In QUEST-RA study, Sokka et al. demonstrated a DAS28 remission rate for usual care of 19.6 %, which is comparable to our findings. Similarly to our study, patients in QUEST-RA were not in a tight control or clinical trial setting, and therefore, remission was not as prevalent as it would be expected in a more intensive treatment strategy [25]. Recently, Santos-Moreno et al. reported that 51 % of long-standing RA patients with moderate or high disease activity treated with synthetic DMARDs under a T2T strategy achieved remission by DAS28 after 6 months of follow-up [28]. In this study, participants had to be moderately or highly active to be included and could not have been treated with three or more synthetic DMARDs previously. Possibly, the sample selection criteria adopted and the shorter follow-up may explain the greater remission rate found by the researchers [28].

Fransen et al. studied 384 patients in 24 centers randomized to either follow a DAS28-oriented intensive or a usual care strategy. After 24 weeks, more patients in the DAS28-oriented centers achieved remission or low disease activity compared to the usual care centers (31 vs. 16 %; $p<0.03$) [4]. Similarly, in our cohort, more patients were at lower disease activity levels after following the T2T strategy. However, the magnitude of this difference was smaller, most likely due to our longer observation time. In addition, the average disease duration of our sample was at least twice higher than in this randomized trial. Joint deformities could dampen disease activity assessment and masquerade a greater improvement.

Despite the lack of radiographic scoring, our study demonstrated that RA patients significantly improved HAQ, a predictor of joint damage. According to our data, even in long-standing disease, intensive synthetic DMARDs use to the lowest RA activity levels improves functionality in 27.1 % of patients over time. As no biologic DMARDs were prescribed, the gain in functional capacity comes with lower drug-related direct medical costs.

In conclusion, our cohort study indicates that T2T strategy in long-standing RA patients with synthetic DMARDs aiming at remission or low disease activity level is effective and feasible in daily practice. Further real-world studies may contribute to better understanding clinical and social impacts of the intensive T2T approach to RA patients.

Disclosure None.

References

1. van Tuyl LH et al (2008) Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90 % remission in a pilot trial. Ann Rheum Dis 67(11):1574–7
2. Verstappen SM et al (2007) Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer assisted management in early rheumatoid arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 66(11):1443–9
3. Grigor C et al (2004) Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 364(9430):263–9
4. Fransen J et al (2005) Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. Ann Rheum Dis 64(9):1294–8
5. Goekoop-Ruiterman YP et al (2005) Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 52(11):3381–90
6. Hetland ML et al (2008) Aggressive combination therapy with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheumatoid arthritis: second-year clinical and radiographic results from the CIMESTRA study. Ann Rheum Dis 67(6):815–22
7. Saunders SA et al (2008) Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. Arthritis Rheum 58(5):1310–7
8. Verschueren P, Esselens G, Westhovens R (2008) Daily practice effectiveness of a step-down treatment in comparison with a tight step-up for early rheumatoid arthritis. Rheumatology (Oxford) 47(1):59–64
9. Moreland LW et al (2012) A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of early aggressive rheumatoid arthritis trial. Arthritis Rheum 64(9):2824–35
10. Schipper LG et al (2011) 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 71(6):845–50

11. Mottonen T et al (1999) Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 353(9164):1568–73
12. Jurgens MS, Welsing PM, Jacobs JW (2012) Overview and analysis of treat-to-target trials in rheumatoid arthritis reporting on remission. Clin Exp Rheumatol 30(4 Suppl 73):S56–63
13. Pincus T, Castrejon I (2013) Evidence that the strategy is more important than the agent to treat rheumatoid arthritis. Data from clinical trials of combinations of non-biologic DMARDs, with protocol-driven intensification of therapy for tight control or treat-to-target. Bull Hosp Jt Dis 71(Suppl 1):S33–40
14. Smolen JS et al (2010) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 69(6):964–75
15. Sokka T, Pincus T (2009) Rheumatoid arthritis: strategy more important than agent. Lancet 374(9688):430–2
16. Bakker MF et al (2012) Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med 156(5):329–39
17. Montecucco C et al (2012) Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study. Arthritis Res Ther 14(3):R112
18. Ling E et al (2013) Outcome of patients with rheumatoid arthritis: cross-sectional study of a single-center real-world inception cohort. Isr Med Assoc J 15(12):758–62
19. Buch MH et al (2013) Creative trial design in RA: optimizing patient outcomes. Nat Rev Rheumatol 9(3):183–94
20. Arnett FC et al (1988) The american rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31(3):315–24
21. Maska L, Anderson J, Michaud K (2012) Measures of functional status and quality of life in rheumatoid arthritis: health assessment questionnaire disability index (HAQ), modified health assessment questionnaire (MHAQ), multidimensional health assessment questionnaire (MDHAQ), health assessment questionnaire II (HAQ-II), improved health assessment questionnaire (improved HAQ), and rheumatoid arthritis quality of life (RAQoL). Arthritis Care Res (Hoboken) 63(Suppl 11):S4–13
22. Anderson JK et al (2011) Measures of rheumatoid arthritis disease activity: patient (PtGA) and provider (PrGA) global assessment of disease activity, disease activity score (DAS) and disease activity score with 28-joint counts (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), patient activity score (PAS) and patient activity score-II (PASII), routine assessment of patient index data (RAPID), rheumatoid arthritis disease activity index (RADAI) and rheumatoid arthritis disease activity index-5 (RADAI-5), chronic arthritis systemic index (CASI), patient-based disease activity score with ESR (PDAS1) and patient-based disease activity score without ESR (PDAS2), and mean overall index for rheumatoid arthritis (MOI-RA). Arthritis Care Res (Hoboken) 63(Suppl 11):S14–36
23. Fransen J, Creemers MC, Van Riel PL (2004) Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology (Oxford) 43(10):1252–5
24. Aletaha D et al (2005) Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum 52(9):2625–36
25. Sokka T et al (2008) Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries. Arthritis Rheum 58(9):2642–51
26. Dale J et al (2014) Tightening up? Impact of musculoskeletal ultrasound disease activity assessment on early rheumatoid arthritis patients treated using a treat to target strategy. Arthritis Care Res (Hoboken) 66(1):19–26
27. Colebatch AN et al (2013) EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis 72(6):804–14
28. Santos-Moreno PI et al (2015) Treatment of rheumatoid arthritis with methotrexate alone and in combination with other conventional DMARDs using the T2T strategy. A cohort study. Clin Rheumatol 34(2):215–20