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Review Article

Treat to Target Strategy in Rheumatoid Arthritis: Real Benefits☆

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ABSTRACT

Treating rheumatoid arthritis (RA) with a goal or "treat to target" strategy is a therapeutic proposal taken from cardiovascular and endocrine literature. It proposes that the therapeutic target in RA should be a state of remission, or an alternative goal could be a low disease activity. Rheumatologists should measure and register disease activity in every clinical visit and if the goal has not been reached, therapeutic adjustments should be made. Current evidence from clinical trials and a meta-analysis supports the notion that this strategy has important clinical benefits in patients with early RA when compared with routine care. It is also described that using protocolized treatment offers greater benefits. Recent data from Dutch cohorts are presented showing its successful implementation. A discussion is offered on the need of more studies in established RA.

Estrategia «*treat to target*» en la artritis reumatoide: beneficios reales

Palabras clave:
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RESUMEN

El tratamiento de la artritis reumatoide con un objetivo o estrategia «*treat to target*» es una propuesta importada de la literatura cardiovascular y endocrina. Se propone que la meta terapéutica en artritis reumatoide debería ser la remisión clínica o alternativamente un estado de bajo nivel de actividad clínica. El reumatólogo debería medir y documentar la actividad de la enfemedad en cada visita y, si el paciente no ha alcanzado la meta deseada, deberían hacerse los ajustes terapéuticos para lograrla. Las evidencias actuales en ensayos clínicos y meta-análisis apoyan que esta estrategia tiene beneficios clínicos importantes en pacientes con artritis reumatoide temprana cuando se compara con el tratamiento médico habitual. También se describe que el utilizar un tratamiento protocolizado reporta mayores beneficios. Se presentan elementos de una implementación exitosa en cohortes de artritis reumatoide temprana en Holanda. Se discute la necesidad de tener más información del beneficio en pacientes con artritis reumatoide establecida.

Introduction

The identification of therapeutic targets and the management of patients with the idea of reaching and maintaining remission has enabled major advances in the treatment of hypertension, diabetes and dyslipidemia, and has led to better clinical outcomes.[1] That experience coupled with additional factors such as the understanding that patients with rheumatoid arthritis should be diagnosed early, and should be treated until achieving the best possible control of the disease, involving elements for measuring clinical disease activity and important advances in therapeutics in the past 12 years, led a group of rheumatologists and patients to propose four general principles and 10 recommendations that were discussed in depth by 60 experts and 5 patients from various countries to develop a consensus and the publication of a strategy called "treat to target".[2] This proposal was received with enthusiasm by the international community[3] and a version with simpler wording exists for patients.[4]

The objective of this review is to present the results available in the literature that assess the real benefits of this proposal.

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To better understand this we briefly present some operational definitions, describe some methodological considerations and list the basic elements of the 'treat to target' strategy, discuss the results of the major studies that have been used and finally discuss some obstacles in its implementation in daily practice.

Operational Definitions

The literature on the subject contains elements that refer to the same concept under different names. If one carefully reviews the term "treat to target" and the strategy of "tight control" (strict control), they both describe the same topic. Both try to get the patient to adequately control their disease by having a good therapeutic target identified. If the objective is not achieved, patient communication should lead to appropriate therapeutic adjustments at each visit until achieved. It seems more appropriate that "treat to target" is written in English, because this well could be clearer than its translation into Spanish and other languages. The author of this review assumes the error and the responsibility of the use of the Anglicized term.

Methodological Considerations

The international team that designed this strategy initially proposed a clear concept of what they wanted to investigate, but the medical literature was reviewed and studies with different designs were found. Without doubt, the best design to assess therapeutic efficacy is the controlled trial by far, or better yet the meta-analysis of randomized trials. This design compares two or more interventions, preferably analyzed in blinded fashion and with clear outcomes for patients groups. One of the major constraints in identifying strategic studies is that the traditional design assigns patients to an intervention that usually remains stable throughout the duration of the study. In some studies, the design allows rescue treatment for patients who have not achieved the desired goal. At the end of the project the number of patients achieving the goal (e.g. ACR20 response) are analyzed but no effort is made at each visit to modify the treatment regimen if this goal has not been reached. It should be understood that the "treat to target" strategy implies the use of a dynamic methodological design, where therapeutic adjustments are made in each visit if the initially proposed goal has not been achieved. A comparison group where other patients received usual clinical management must also exist. Intervention groups (strict control) and the comparison group should be similar and it is intended that the only thing that distinguishes them is the intervention to which they were assigned.

There are certainly other variables to be analyzed: the duration of the disease, the intensity of interventions, the set goal, the frequency of visits, the duration of the study, the time to reach the goal and maintenance of long-term goal and clinical, functional and structural intervention consequences.

Key Elements of the 'Treat to Target' Strategy

The original[2] publication proposed as key elements that the management of patients with RA should have a clear goal and this be agreed upon between the patient and the rheumatologist. The goal to which both should aspire is remission, or in other cases an acceptable alternative goal is to achieve a low level of clinical activity. The degree of disease activity should be measured at each visit with composite indexes that include joint counts and the clinician must act accordingly if the goal has not been reached. The proposal presents an algorithm which emphasizes the importance of achieving the goal and suggests the frequency of visits (every month in many cases with clinical activity and every 3 months once the goal is reached). The algorithm points out the importance of achieving and maintaining the goal. This strategy is flexible because, in some of the points mentioned, it is important to take into account comorbidity that may cause the strict goal to not be achieved in some patients due to the additional risk that might be a consequence of polypharmacy and its side effects. It also emphasizes the importance of measuring functional and structural damage.

Evidence of its Usefulness in Clinical Trials

We reviewed two publications with different search criteria, a strategy based on "treat to target"[5] and a meta-analysis that provided data on the usefulness of this approach.[6]

Studies Reviewed to Propose the Strategy 'Treat to Target'

Schoels Monika advised by two researchers conducted a systematic review of the medical literature to find the elements that could support this strategy. This search was made in Medline, Embase and Cochrane from the date of its implementation until December 2008. They also reviewed the abstract books of the American College of Rheumatology and European meetings of 2007 and 2008. The search was limited to humans, adults and English publications. Five thousand eight hundred and eighty-one titles were reviewed and 76 items were considered potentially useful. Twenty four articles or abstracts that apparently could have studied the strategy "treat to target" were subsequently analyzed and seven strategic intervention studies finally detected: in four of these patients were randomized to a group with a clear goal and a another group of patients to usual management; 2 more compared two different randomly assigned goals and one of them used a historical control. They describe only the results of the studies published in extensive non-pilot studies comparing an experimental group with a control group concurrently.

a) The TICORA (Tight Control of Rheumatoid Arthritis) study clearly illustrates the benefits of tight control strategy in patients with rheumatoid arthritis.[7] Grigor et al. randomly assigned 110 patients with rheumatoid arthritis to 2 intervention groups of 55 patients each, who would be evaluated every month. The strict control group had a clear objective, to achieve a DAS 28 < 2.6 and if that goal was not reached, the physician adjusted medical treatment that included increased doses of disease-modifying drugs (DMARDs), combinations thereof (methotrexate, sulfasalazine, and gold salts) and even swollen joint infiltrations. The control group received usual medical management without a clear goal. The results of this study showed that at 18 months the odds were in favor of the strict control group:

   EULAR good response: 82% in the strict control group versus 44% in the control group, RM 5.8 (95% CI: 2.4–13.9), *P*<.0001.

   Referral: 64% in the strict control group versus 16% in the control group, RM 9.7 (95% CI: 3.9–23.9), *P*<.0001.

   ACR70: 71% was achieved in the strict control group versus 18% in the control group, RM 11 (95% CI: 4.5–27), *P*<.0001.

   HAQ: decreased 0.97 ± 0.8 in the strict control group versus -0.47 ± 0.9 in the control group, *P*=.002.

   Radiological changes (median and interquartile range):

Total score: 4.5 (1–9.8) in the strict control group versus 8.5 (2–15) in the control group, *P*=.02.

Joint space narrowing 3.2 (1.1–7.5) in the strict control group versus 4.5 (1.5–9), *P*=.3.

Radiological progression of erosions: 0.5 (0–3.3) in the strict control group versus 3 (0.5–8.5) in the control, *P*=.002.

b) CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis).[8] This open, controlled study compared two interventions: a group of 151 patients who were evaluated for tight control each month based on swollen joint count, tender joint count, ESR and patient global assessments. If the patient had not obtained an improvement of at least 20% in the swollen joint count and at least 2/3 of the other measurements, a computer suggested a therapeutic adjustment to the physician. The endpoint was defined as treatment failure or not having achieved at least a 50% improvement when compared with initial evaluations. The control group of 148 patients was followed every 3 months depending on the clinical judgment of the treating physician performing the therapeutic interventions. In both cases the elements available were ascending doses of methotrexate with subcutaneous administration of cyclosporine A.

The outcome of interest was to achieve remission for 3 consecutive months. The results of this study showed that the number of patients achieving remission at one year was 35% in the intensive management and therapeutic adjustment by computer versus 14% in the control group, *P*<.001. At 2 years the group therapeutic adjustment by computer achieved remission in 50% versus 37% in the control group, *P*<.02.

The mean time to achieve remission was 10.4 months (95% CI: 9.1–11.7) in the intervention group versus 14.3 months (95% CI: 12.6–16.1) in the control group, *P*<.01.

The average duration of all periods in remission was 11.6 months (95% CI: 10.1–13.1) in the intervention group versus 9.1 months (7.6–10.6) in the control group, *P*=.02.

ACR50 was reached in 58% of patients in the intervention group at one year versus 43% in the control group, *P*<.01. At 2 years there was no difference between groups on this variable.

This study found neither differences in functional capacity as measured by the HAQ nor radiological progression.

c) Fransen et al.[9] This study compared 205 patients with treatment aimed to achieve a DAS28<3.2 versus 179 patients who were treated based on clinical judgment of their rheumatologist. In both cases the patients were initially re-evaluated after one month, two months, three months and then every 3 months, receiving treatment with traditional DMARDs. The outcome of interest was measured at 24 weeks. DAS28<3.2 was achieved in 31% of the intervention group versus 16% in the control group, *P*=.02. The mean DAS28 and standard deviation decreased in the former group -0.4 ± 1 and 1.2 ± -0.14 in the control group, *P*=.36. Twenty percent of patients in the intervention group changed DMARDs and only 9% in the control group, *P*=.01. There was no difference in functionality and no radiological progression was evaluated.

d) Symmons et al.[10] studied 233 patients assigned to an intervention group who were evaluated at least every four months with the goal of bringing the patient to a lower than twice the upper normal value of CRP, and also sought to have no joint swollen or painful joints. The control group included 233 patients who were followed at least every four months, looking symptom control with routine management. Results are reported at three years and showed that significant differences in means and 95% CI were found in the overall assessment of the evaluator: 3.76 (0.03–7.52), *P*=.045 and the evaluation rheumatoid arthritis overall: 0.41 (0.01–0.71), *P*=.010.

No differences in the number of swollen or painful joints, ESR or physician global assessment were seen. There were no differences in the functional capacity after up to 3 years. Radiological progression occurred in both groups and was significant only in the control group (*P*=.03).

Results of a Meta-analysis

Schipper et al.[6] published in 2010 the results of a meta-analysis of six trials that compared a group with strict control strategy compared to a control group that followed the usual medical management of the rheumatologist. We included studies identified from January 1995 to August 2009. The selection criteria were the following items: a) studies comparing a strategy of tight control versus usual care, b) patients with rheumatoid arthritis according to the 1987ACR criteria, c) that treatment include at least used DMARDs, anti-TNF or glucocorticoids, d) that the study measure clinical efficacy, and e) the primary or secondary outcome include DAS or DAS28.

Its objectives were to evaluate whether strict treatment offered therapeutic advantages over usual standards of care and determine if the strict control group with a treatment protocol was better than no treatment.

It is interesting to note that not all studies described in Schoels work were included in the meta-analysis because the selection criteria were different. The authors describe in a careful way the characteristics of 6 trials, 3 of them with intense treatment analyzed. The results are inconclusive in the sense that intensive treatment is better than current management and that the average difference in DAS28 was 0.59, *P*<.001. They also showed that this benefit is greatest when carrying out a treatment protocol with a difference of 0.97 in DAS28 values compared to 0.25 in the no treatment protocol, *P*<.001.

The authors argue that all studies in the strict management group were made in early rheumatoid arthritis patients with short duration of disease, DMARD-naive and with high levels of activity[7,8,11] and common management groups included in patients with established, long-lasting rheumatoid arthritis, with several previous treatment with DMARDs and a lower level of clinical activity. This certainly implies that different populations may directly influence the results and limit the extrapolation of results to all patients with rheumatoid arthritis. They discuss the importance of using protocolized treatments in established rheumatoid arthritis.

Of these six studies, four of them were randomized and 4 were done in the Netherlands. This raises a cautionary note regarding the heterogeneity of these six studies. Results mentioned are especially important in all TICORA[7] study outcomes and postulate that steroid infiltration in inflamed joints at each visit and monthly monitoring could explain these results. Radiographic improvement was observed in two of the 6 studies.[7,11]

The authors conclude that measurement of clinical activity and the protocolized therapeutic setting improve clinical outcomes in rheumatoid arthritis. This is especially true in early rheumatoid arthritis. They question how best to proposed therapeutic strategy in the treatment protocol.

Evidence of Implementation

The information available in the medical literature mentioning that early diagnosis, early treatment and improved outcomes in severe rheumatoid arthritis led to the design of a Dutch cohort, DREAM (Dutch Rheumatoid Arthritis Monitoring Remission Induction Cohort Study) in order to analyze the achievement of clinical remission. The study, published in 2011, presents the results of this strategy.[12]

It included 534 patients from five hospitals with the diagnosis of rheumatoid arthritis of less than one year of development, older than 18 years, with DAS28>2.6 and naive to treatment with DMARDs or steroids. These patients were evaluated according to a protocol at 4, 8 or 12 weeks. The paper presents the results of remission rates (based on modified ARA DAS28 remission criteria) and good response according to EULAR, at 6 and 12 months.

All patients were treated according to an algorithm that starts with 15 mg of methotrexate, scaled to 25 mg if remission is not achieved, with sulfasalazine added later, and switched to anti-TNF if no improvement is seen and failure to DMARDs (DAS28<2.6) and anti-TNF (DAS28<3.2) criteria are established at each visit.

The data show that at 6 months (491 patients), management toward the goal or "treat to target" with DAS28 remission was achieved in 47% and this figure rose to 58.1% at 12 months (389 patients). The EULAR response at 6 months showed there was a good response in 57.6% of cases and this figure reached 67.9% at 12 months. Data with the same trend were observed with the old ARA definition modified by the authors (32% at 6 months and 46.4% a year).

The authors conclude that the 'treat to target' strategy is feasible and the results offered by this cohort of patients with early rheumatoid arthritis are very encouraging.

A recent publication[13] compared 2 Dutch cohorts of early rheumatoid arthritis patients who met the American College of Rheumatology criteria. One included 126 patients and was designed to achieve clinical remission (DAS28<2.6) and included a step-up treatment protocol and methotrexate, sulfasalazine and sulfasalazine replacement by anti-TNF therapy in case of failure. The second cohort included 126 patients who were treated with methotrexate or sulfasalazine without a DAS28 therapeutic target < 2.6. The outcome of interest per year was the percentage of patients achieving clinical remission in each group and time to remission was considered a secondary outcome. It was found that 55% of patients in the strict control strategy achieved remission compared with 30% of patients in the usual care cohort (OR: 3.1, 95% CI: 1.8–5.2). The median time to remission was 25 weeks in the strict control group versus 52 weeks in the usual care group (P<.0001). The DAS28 decreased 2.5 in the strict control group versus −1.5 in the normal treatment group (P<.0001). The authors concluded that strict control achieved remission in a faster and more frequent way in patients with early rheumatoid arthritis.

Limitations for Implementation

This review presents sufficient evidence to conclude that the treat to target "strategy" is particularly useful in patients with early rheumatoid arthritis. It highlights the importance of clinical activity measurement at each visit and docketed therapeutic setting that translate into better clinical, functional and radiological outcomes. The different clinical and health systems should be analyzed in their environment to determine which is the best protocol. It is important to note that most of the studies reviewed reached very good results without the use of biological agents and that the most recent studies were included in their treatment algorithm. Lack of information impeded the conclusion of whether the 'treat to target' strategy with protocolized management will have the same results in patients with established rheumatoid arthritis and in other settings without the organization of the Dutch studies. The dissemination and acceptance of this strategy, analysis of obstacles, strategies for implementation and the scope of the same in the different health systems should be checked periodically.

Ethical disclosures

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

Confidentiality of Data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflict of Interest

The authors have no conflict of interest to make.

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