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COMMENTARY

Treat-To-Target and Treat-To-Budget in Rheumatoid Arthritis: Measuring the Value of Individual Therapeutic Interventions

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Abstract: Treat-to-target (T2T) and dose tapering after obtaining the therapeutic objective (called "treat-to-budget"-T2B-in this Commentary) are the two most commonly used therapeutic strategies in rheumatoid arthritis. In theory, both strategies could add value to the healthcare system, although they are focused on different objectives: T2T strategy improves outcomes but increases short-term costs, while the cost savings obtained through T2B are associated with higher relapse rates. The systematic implementation of both strategies must be founded on solid evidence of their effectiveness and efficiency. However, the level of evidence between guidelines and individual studies is inconsistent for both strategies and the number and the quality of cost-effectiveness analyses is scarce. Raising the level of evidence requires a move from generalization to individualization by conducting randomized clinical trials that assess each of the many strategies that fall under the umbrella of the overall T2T and T2B concepts. In addition, such studies should consider the therapeutic goals and impact of the disease from the perspective of individual patients, which is only possible by promoting shared decision-making.
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Key Summary Points

Treat-to-target (T2T) and dose tapering after obtaining the therapeutic objective ("treat-to-budget"-T2B-) are the two most commonly used therapeutic strategies in rheumatoid arthritis.

The systematic implementation of both strategies must be founded on solid evidence of their effectiveness and efficiency.

However, the level of evidence between guidelines and individual studies is inconsistent for both strategies and the number and the quality of cost-effectiveness analyses is scarce.

Raising the level of evidence requires a move from generalization to individualization by conducting randomized clinical trials that assess each of the many strategies that fall under the umbrella of the overall T2T and T2B concepts.

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by its high prevalence and substantial impact on society and health services. Over the last decade, the systematic use of reliable tools for clinical evaluation, the development of targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), and the implementation of new therapeutic strategies have all contributed to a significant improvement in the prognosis of RA [1]. At present, the two most commonly used treatment strategies are treat-to-target (T2T) and dose tapering after obtaining the therapeutic objective.

The aim of T2T is to achieve clinical remission or at least a low level of disease activity. The implementation of T2T requires an early diagnosis and must be based on a joint decision made by the doctor and the patient. Disease activity must also be tightly controlled through regular treatment adjustments to reach the therapeutic target. Tapering involves reducing the dose, or increasing the interval between doses, in patients who have achieved remission or a low disease activity. Tapering aims to maintaining the therapeutic goal but at the same time decreasing the risk of adverse effects and the cost of treatment, thereby contributing to the sustainability of healthcare systems, so this strategy could also be dubbed as "treat-to-budget" (T2B). The literature contains excellent reviews of both strategies [2–4].

In theory, the combined use of T2T and T2B could add value to the healthcare system. According to Porter's well-known definition of value, healthcare systems should seek the best health outcomes achieved per dollar spent [5]. Each of the strategies helps improve one of the two components in Porter's equation, but they can also have a negative impact on the other component. There is evidence suggesting that the T2T strategy improves outcomes, but increases short-term costs; [6] while on the other hand, the cost savings obtained through T2B are associated with a higher relapse rate [7] (Table 1). Given this, the clinical and economic impact of using both strategies, either separately or in combination, cannot be analyzed independently. The total cost (not just the drug-related cost) and clinical outcomes of each strategy must be compared before drawing conclusions about their value. In other words, the cost-effectiveness of T2T and T2B must be analyzed to determine their value.

Most publications into RA management support the use of T2T over that of the usual treatment [2]. The T2T approach has been adopted by the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR) and the Asia Pacific League of Associations for Rheumatology (APLAR) [4], although the level of evidence (LoE) between the guidelines is inconsistent. For instance, the LoE in the EULAR guidelines lies between 1a and 2b, depending on the type of recommendation [8], while it is low or moderate in the ACR guidelines, depending on the type of patient [9]. An exhaustive review by the National Institute for Health Research UK concluded that there was mixed evidence for T2T and only observed clinical benefits in specific patient groups (early RA) for some outcomes [10]. The discrepancy between the guidelines and various individual studies that compare T2T against routine treatment should not come as a surprise. These differences can be explained by the high heterogeneity of the studies, which assessed different types of patients and included distinct study designs, treatment regimens, response criteria, and variables.

T2T increases short-term healthcare costs, however very few researchers have assessed the strategy's efficiency [11] and even those were low-quality studies [10]. A robust evaluation of efficiency would need to analyze the incremental cost-effectiveness ratio [expressed as additional cost per quality-adjusted life year (QALY) gained] for each of the many treatment regimens that fall under the T2T concept in order to check if the cost per QALY gained lies below commonly accepted cost-effectiveness thresholds.

With respect to tapering, the relapse rate depends on the dose reduction regimen, but it is often above 30%, one year after treatment [7]. Different studies show that better outcomes are obtained in patients in sustained remission for at least 6 months and dose reduction or an increase in dosing interval are preferable to treatment discontinuation [12]. It is also known

Table 1 Some differentiating characteristics of treat-to-target and treat-to-budget strategies

	Treat-to-target	Treat-to-budget
Main focus	Patient	Healthcare system (payer)
Main objective	Improves outcomes	Reduces costs
Potential negative consequence	Increases cost	Reduces effectiveness
Scope of the strategy	Wide (diagnosis, patient care, treatment, etc.)	Narrow (drugs)
Level of evidence	Moderate–High	Low–Moderate
Degree of implementation	Low–Moderate	Moderate–High
Evidence of cost-effectiveness	Scarce	Scarce
Value approach	Incremental cost-effectiveness	Decremental cost-effectiveness

that when relapse occurs, patients respond well to reintroduction of the same drug [12]. It should be noted that most of the evidence on tapering comes from observational studies with a small sample size and only a third are based on randomized clinical trials [7]. A recent single-blind, randomized clinical trial found relapse rates of 33% and 43% ($p = 0.17$) in the first year after reducing the dose of TNF inhibitors and conventional synthetic DMARDs (csDMARDs), respectively [13]. While it is widely accepted that higher doses of biological agents are associated with a greater risk of infection, it is remarkable that tapering studies do not evaluate the decrease in adverse effects before and after applying the strategy, which proves very revealing about the main aim of dose reduction, which seems to focus mostly on impact on efficacy.

The level of evidence and strength of recommendation for the T2B approach in the main guidelines (ACR, EULAR) is at best moderate (2b) and there are no indications as to which is the most appropriate tapering strategy [3, 8, 9]. In contrast to the T2T strategy, which is less widely implemented [14] despite support from a greater LoE, the degree of T2B implementation is relatively high (Table 1) [15, 16], probably because it is easier to put into practice and requires less resources than T2T.

Tapering studies feature a broad heterogeneity in dose reduction regimes, follow-up time, and patient type [7]. There is therefore a need to assess the effectiveness of each dose reduction schedule for each specific drug, while continuing to make progress in the study of predictors of low disease activity and remission to identify which patients might benefit the most from tapering. To date, very few antirheumatic drugs include information on dose reduction results in their summary of product characteristics [17].

Several studies have estimated the direct savings in drug costs derived from tapering, but practically none of them have evaluated its cost-effectiveness [18]. Given that dose reduction tends to increase the rate of relapses, future studies should contemplate a decremental cost-effectiveness analysis, whose results are expressed as cost saved per quality-adjusted life year lost. These results should help decide whether the savings associated with the strategy offset the potential for clinical deterioration [19]. One study used this approach and reported a savings of €390,493 per QALY lost and therefore concluded the strategy was highly effective [20]. However, we cannot assume this finding is true for all tapering regimes because in the given study the dose reduction was not accompanied by a significant increase in relapses, which is unusual compared to most other tapering studies [7].

We are currently experiencing a trend for a convergence between evidence-based and patient-centered medicine [21]. The adoption of strategies such as T2T and T2B should fulfill

both objectives, adding value to individual patients and healthcare systems. However, the systematic implementation of these strategies must be founded on solid evidence of their effectiveness and efficiency. Raising the level of evidence requires a move from generalization to individualization by conducting randomized clinical trials that assess each of the many strategies that fall under the umbrella of the overall T2T and T2B concepts. In addition, such studies should take into account the therapeutic goals and impact of the disease from the perspective of individual patients, which is only possible by considering their perspective and promoting shared decision-making.

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