Best Practice & Research Clinical Rheumatology 36 (2022) 101735

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

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Treating-to-target in rheumatology: Theory and practice

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Keywords:
Remission induction
Patient-reported outcome measures
Treatment outcome
Person-centred care
Overtreatment
Dual-target strategy

A B S T R A C T

Despite its inclusion in current treatment recommendations, adherence to the treat-to-target strategy (T2T) is still poor. Among the issues are the definition(s) of target, especially the caveats of the patient global assessment (PGA), included in all recommended definitions of remission. The PGA is poorly related to inflammation, especially at low levels of disease activity, rather being a measure of the disease impact. Up to 60% of all patients otherwise in remission still score PGA at >1 and as high as 10. These patients (PGA-near-remission) are exposed to overtreatment if current recommendations are strictly followed and will continue to endure significant impact, unless adjuvant measures are implemented.
A proposed method to overcome both these risks is to systematically pursue two targets: one focused on the disease process (the biological target) and another focused on the symptoms and impact (the impact target), the dual-target strategy. Candidate instruments to define each of these targets are discussed.

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https://doi.org/10.1016/j.berh.2021.101735
1521-6942/

Treat-to-target

The treat-to-target (T2T) strategy refers to a set of principles to guide treatment decision making by aiming to achieve prompt and persistent control of a particular chronic condition. The cornerstones of this strategy include the definition of a target of a therapy (a predefined disease status, most often remission), frequent assessments of disease activity with validated measures and regular adjustments of the treatment plan as needed to achieve and maintain the target [1]. This, naturally, entails the consideration of patients' clinical characteristics and the active involvement of patients in treatment decisions and planning [1].

This strategy has been highly successful in different areas of medicine, such as hypertension [2] and diabetes [3], resulting in significant prevention of damage, disability and premature mortality.

This concept was transferred to rheumatology, first to rheumatoid arthritis (RA) management and subsequently to several other rheumatic and musculoskeletal diseases (RMDs), such as spondylarthritis, gout and systemic lupus erythematosus [4].

T2T in RA and its reported impact

The T2T strategy for managing RA was proposed in 2010 [5] and updated in 2014 [6]. It was incorporated into European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) recommendations for RA management since 2010 and 2012, respectively [7,8].

The current guidelines postulate that remission (or at least low disease activity – LDA), defined according to the Simplified or Clinical Disease Activity Index (SDAI/CDAI) or the ACR/EULAR Boolean-based definition, should be the target of treatment in every person with RA [7]. Patients should be assessed every 3–6 months, using composite measures of disease activity, and therapy should be adjusted/increased as needed to achieve and maintain the target. Individual patient factors, such as comorbidities, should be considered, and decisions should be made together with the patient in a shared-decision manner [7,8].

Remission was selected as the primary target as it provides the best possible chance to reduce symptom severity, halt structural joint damage, reduce the risk of comorbidities (e.g. cardiovascular disease) and improve the quality of life (QoL) of patients with RA [9,10].

There is plenty of evidence of the superiority of T2T, compared with routine/standard care, regarding several RA outcomes, with emphasis on the rates of remission. The TICORA [11] and the CAMERA [12] trials showed that T2T yields a higher proportion of DAS28 remission (50–65% vs 16–37%). In the recent "Norwegian Very Early Arthritis Cohort 2.0 (NOR-VEAC2.0)" study, a 2y SDAI remission rate of 46% was achieved using T2T, compared with the 31% rate achieved in the routine care cohort (pre-T2T) [13]. Ramiro et al. [14] showed that in daily clinical practice, the correct application of a T2T strategy in patients with RA leads to higher rates of remission, even when considering more stringent definitions of remission (CDAI or SDAI). The T2T approach was also associated with higher rates of patients without radiographic progression [1,11,15].

The implementation of T2T also proved to be a valuable target from the patient's perspective: it provides superior efficacy in terms of pain control or improving physical function, physical wellbeing, work productivity and health-related QoL, both in clinical trials [11] and observational studies [14,15].

From a societal perspective, the T2T strategy was found to be cost-effective, using real-life data from the DREAM registry and the Nijmegen early RA inception cohort [15] and also inferred from a systematic review [16].

T2T in clinical practice

Despite all these advantages, different international studies have confirmed a low adherence to the T2T principles and little change in clinical practice [17–19]. Data from the CORRONA registry, in the USA, demonstrated that less than 50% of RA patients under non-biological DMARDs received care consistent with T2T recommendations [17]. More than 50% of all patients under anti-TNF therapy were still receiving the same drug despite inadequate response at 6 or 12 months [20]. A recent meta-

analysis, including data from real-world studies, determined that DAS28 remission was only achieved by 17.2%,16.3%, 21.5% and 23.5% of all RA patients at 3, 6, 12 and 24 months, respectively [21].

Several barriers have been invoked to explain this. Electronic health records do not generally facilitate the use of these measures, hindering their application [22]. Difficulties in communication between healthcare providers and patients and/or healthcare regulators have also been pointed out as barriers to T2T implementation. Physician's age, professional experience and clinical setting as well as personal opinions regarding drug efficacy have been shown to be relevant. Economic aspects and accessibility of medications, as well patient's preferences and specific factors, such as comorbidities, have also been highlighted as obstacles [1,23].

In addition, there is an increasing concern regarding the possibility that strict adherence to the T2T principles, as expressed in current recommendations, may lead to a considerable risk of overtreatment, due to fragilities in the definition of the stated target [24,25].

Definitions of target: the patient global assessment's dilemma

The definition of a target is the central pillar of the T2T strategy: it should be valid (regarding the purpose in mind, i.e. minimizing disease impact and halting structural damage), feasible, safe and well-accepted to be pursued in clinical practice.

The provisional definitions of remission, proposed conjointly by an ACR and EULAR task force, recommended the use of either a Boolean-based definition or a maximum score in SDAI [26]. Both include the patient global assessment (PGA) of disease activity as the sole patient-reported outcome measure (PROM). The Boolean definition requires that tender and swollen 28-joint counts (TJC28/SJC28), C-reactive protein (CRP, in mg/dl) and PGA (0–10 numerical rating scale) are all $\leq$1. The SDAI score (simple sum of the 4 Boolean criteria + the Physician's Global Assessment of Disease Activity –- PhGA) should be at a maximum of 3.3. Another definition was considered suitable for clinical practice if CRP is unavailable: a maximum CDAI score (the same as SDAI without CRP) of 2.5. Although these definitions were specifically designed for clinical trials, their use in clinical practice was already predicted in the original publication, and they were rapidly adopted in practices around the world, especially in Europe.

These target descriptions highlight the importance of PGA in all definitions: 1 point in the PGA has the same weight as a measure of disease activity, i.e., inflammation as 1 tender or 1 swollen joint or 1 mg/dl in CRP levels.

The meaning of PGA

PGA has been the core of the most substantial controversies surrounding the definitions of target over the recent years. The main arguments revolve around whether PGA reflects actual disease activity reliably enough to play a crucial role in guiding immunosuppressive therapy.

There is extensive and consistent evidence to demonstrate that PGA is more a measure of symptom severity and disease impact than a true reflection of disease activity. PGA is essentially driven by pain (whatever its origin), physical function, fatigue, sleep and psychological issues, bearing little relationship with objective measures of inflammation [27–32]. Comorbidities, such as depression, fibromyalgia or other painful conditions, as well as health literacy and background culture, may influence patient assessment [28,33]. In addition, PGA has been conveyed by several different formulations, leading to variability in answers, affecting the estimated remission rates [34,35]. Patients have difficulties in rating PGA as a continuous score, mainly due its subjective nature [33,36,37], and they are usually not briefed on the concept or its intent.

PGA has been shown to distinguish active treatment from control when analyses are performed at the group level in clinical trials with high levels of disease activity at baseline [26]. However, its ability to gauge inflammation becomes lower as disease activity improves resulting in lower levels of inflammation [38,39], exactly when the tough decisions based on the target are to be made. Moreover, these decisions are made individually, placing further stress on the ability of PGA to help distinguish those patients who have reached the target from those who need additional immunosuppression.

PGA-near-remission: rates and implications

Recent meta-analyses have shown that a considerable proportion of patients in clinical trials and clinical practice fail to achieve ACR/EULAR Boolean-based remission solely due to PGA>1. This status (SJC28, TJC28, and CRP (in mg/dl) all $\leq$1 and PGA>1), termed PGA-near-remission [28], was observed in 19% of all patients included in clinical cohorts [40] and randomized trials [41], compared with 12% and 23% of patients achieving "full" remission, respectively. This indicates that as many as 60% of all patients otherwise in remission have a PGA>1. Patients in PGA-near-remission have PGA levels that are similar to patients in non-remission, but they are indistinguishable from those in full Boolean-remission regarding other indicators of disease activity.

This shows that bringing patients into remission provides a substantial contribution towards the abrogation of disease impact but does not guarantee that this is achieved.

This is a very significant problem that requires immediate attention. In fact, patients in PGA-near-remission cannot be expected to improve with additional immunosuppression, and therefore, this substantial proportion of patients would be exposed to the risk of overtreatment if current T2T recommendations are strictly followed.

Such observations clearly indicate that the inclusion of PGA significantly damages the quality of the treatment target and should be reconsidered.

This conclusion might be overrun if PGA was shown to reflect subclinical inflammation, as suggested by some, or demonstrated to have a positive impact on the performance of the target as a predictor of good radiographic outcome.

PGA, subclinical inflammation and damage accrual

Considering the above data, several authors and scholars have argued that a high PGA by patients otherwise in remission is probably a reflection of subclinical inflammation or involvement of musculoskeletal structures not included in 28 joint counts. This hypothesis was addressed through extensive blind ultrasound evaluation of joints, bursae and tenosynovia of RA patients in remission and in PGA-near-remission. No differences were observed [42], in line with a short report from another group [43].

The issue of damage prediction was the object of a meta-analysis of individual patient data from 11 RCTs (n > 5700): the 3V remission definition (the Boolean definition without PGA) was found to be actually more reliable than the original 4V-remission definition as a predictor of a good radiographic outcome [41]. These results are also supported by data from cohort studies [44,45]. Evidence was also provided that, among those patients in 3V remission, there was no association between the PGA scores and the progression of radiographic damage. Unfortunately, both the 3V and the 4V Boolean definitions of remission were poor predictors of radiographic outcome, with prediction accuracies of 41% and 51%, respectively. This suggests that opportunities to improve this accuracy should be sought.

Could/should we simply exclude PGA from the definition of target?

The need to have the patient's perspective incorporated into the target was one of the arguments leading to the inclusion of PGA in the ACR/EULAR proposal [46]. Considering the patient's perspective is, unarguably, an ethical imperative in medical practice. However, the issue is whether the target used to guide immunosuppressive therapy is the most appropriate vehicle for this.

The data revised above suggests that this induces a considerable risk of overtreatment.

Moreover, having the PGA included in the target may give the practising clinician the unwise impression that the patients' concerns are already incorporated and need no further (detailed) study or intervention. Considering the PGA as a separate target would also be unwise, as it provides no information whatsoever on what is still impacting upon the patient's enjoyment of life and, thus, cannot be used to select the most appropriate adjuvant interventions. In addition, the patient's experience of the disease must still remain core to the disease management objectives.

How can we best serve the two goals? This can be achieved by the following ways: 1. by curtailing damage accrual while minimizing overtreatment and 2. by optimizing the impact of disease upon the patients' life.

Some authors have suggested that this could simply be overcome by raising the PGA cutoff to remission in the Boolean definition to a score of 2 [47]. This would, obviously, reduce the risk of overtreatment, but not to a large degree. We have shown that 51.2% of patients in PGA-near-remission have a PGA score >3, and as high as 10! [39].

The dual-target proposal

Trying to bring all these points together, a proposal has been made [28,48] that two separate targets be considered as guidance in the management of RA: one focused on the disease process (the biological target) and the other focused on the symptoms and impact (the impact target).

Biological target

There is a general consensus that the core objective of the treatment of RA should be, first and foremost, the complete abrogation of inflammation and biological remission, as this provides the best possible assurance of long-term outcomes in terms of structural damage and function. It is also clear that achieving remission as early and consistently as possible plays a decisive role in reducing the impact of the disease upon the patient's life, although it may not be sufficient.

We have demonstrated that a 3V Boolean definition of remission performs better than the current 4V remission in the accurate prediction of a radiographic outcome while reducing the risk of overtreatment. The possibility that excluding PGA from SDAI and CDAI, while adjusting the cutoff values for the definition of remission and LDA, would also provide advantages, warrants research. The hypothesis of a novel 4V-remission definition substituting the PGA by the PhGA also warrants consideration. In fact, the physician's global evaluation seems to be well rooted in the objective signs of inflammation [49]. The physician may also consider various factors that may confound both the “objective” and the subjective measures of disease activity, such as the accompanying inflammatory, painful or disabling conditions, depression and psycho-social features or relevance. We think it is probable that once PGA is removed from the definition, the target should be limited to remission without consideration of LDA, as in current recommendations.

A final decision regarding the optimal definition of the biological target requires extensive dedicated research and peer debate towards a consensus.

Impact target

The definition of the impact target seems more complex. RA has a significant impact in various domains of the patients' lives, e.g. pain, fatigue, function, emotional and physical well-being, participation and sleep, among many others.

The ideal target and its measurement should be valid, reliable, easily understood, relevant from the patients' perspective, feasible, informative towards the selection of potential interventions and responsive to change. It should also be stable enough over time to allow for the consistent pursuit of the target value. The definition of such a target remains unclear and challenging.

PGA is undoubtedly not appropriate to this end, but some available tools seem promising.

- **Patient Acceptable Symptom State (PASS)** is defined as the highest level of symptoms below which the patient would consider it acceptable to live for a certain period [50]. As PASS refers remaining in a given state over time and is answered as “yes or no”, it is meaningful for patients and easy to answer. However, we and others have demonstrated that being in an “acceptable status” corresponds to a degree of disease activity in the range of moderate disease activity and to poor levels of disease impact in different cohorts [51–54]. This is an important limitation given the objective of optimizing outcomes.
- **Patient Experienced Symptom State (PESS)** is assessed through the following question “*Consider how your rheumatic disease has affected you during the last week. If you were to remain in the coming months as you have been last week, how would you rate your condition?”* offering a five-level Likert

scale response (very bad, bad, acceptable, good and very good). PESS has been shown to be valid, with a good correlation with disease activity and other PROMs reflecting different impact domains [55].

Sensitivity to change and reliability needs further assessment. Similarly to PASS, it is a PROM assessed through a simple question about patients' satisfaction with their state of symptoms. However, considering five levels of satisfaction is more discriminative and more easily manageable by the patient. Furthermore, we have shown that the states of "good" or "very good" reflect both LDA or remission of disease activity as well as low levels of impact in the different domains, overcoming the main limitation of PASS. PESS does not identify the domains particularly affected and would require additional evaluations to support treatment decisions. However, it is simple and easy to apply, making it a potentially useful screening tool for patients in need of further assessment.

- **Rheumatoid Arthritis Impact of Disease** (**RAID)** [27] **score,** [56] developed under the auspices of EULAR; the RAID addresses seven domains of impact considered of utmost relevance by patients with RA. These include pain, function and fatigue, considered as core domains, and also sleep, emotional and physical well-being and coping. Each domain is evaluated by the patients using a single 0 (= no symptom) to 10 numeric rating scale (NRS) and has a specific weight used to derive a single integrated RAID score [56]. The RAID was initially designed for use in clinical trials, as a composite index and proved to be feasible, reliable and sensitive to change in different sets of patients [56–58]. However, used as a single score, it does not inform on the most impacted domains, which limits its use in the selection of the most promising therapeutic interventions.
- **RAID.7** This is the most recent development of the RAID, which considers the seven items of RAID separately (RAID.7), thus overcoming the limitation of RAID described above. It has been shown that each of these NRSs can be used independently as tools that are valid, feasible, reliable and sensitive to change [59]. These properties make RAID.7 a promising instrument to assess impact, particularly in clinical practice.
- **The McMaster Toronto Arthritis patient preference questionnaire (MACTAR)** is a functional index that measures change over time in impaired activities selected by each patient in a baseline interview. In addition, it contains questions on the state of physical, social and emotional function and overall health and their relationship with RA. The MACTAR is valid, reliable and responsive to interventions but has limited feasibility [60,61].
- **Goal-Oriented Attainment Scale (GAS):** GAS is a method of scoring the extent to which the patient's individual goals are achieved during interventions. The goals are identified through interviews and weighted according to importance and difficulty. Although each patient has their outcome measure, it is scored in a standardized manner to allow statistical analysis (−2: much worse to 2 "much better"). In GAS, the tasks are individually identified to suit the patient, and the levels are individually set around their current and expected performance levels. GAS has good psychometric properties and has become used in several areas, such as neurology and rehabilitation. A potential limitation is that not all patient goals may be realistic or attainable, and the definition of such goals demands careful professional explanations and negotiations [62].

Selecting the most appropriate impact target tool will still require considerable research and extensive debate and deliberation with solid input from patients. The combination of ideal features described above is not easy to achieve and has not been demonstrated with existing tools.

A pragmatic dual-target approach

Notwithstanding the limitations and evidence gaps described above, we believe it is helpful to delineate how the dual-target strategy could be used in practice (Fig. 1).

While supporting the patient progress from high disease activity to remission, the clinician would primarily chase the biological target while in active disease, as this is also the best possible contribution to reduce disease impact. This could be represented by the 3V Boolean remission described above, the

Fig. 1. Flow of care in a dual-target paradigm (draft). Patients with active disease start DMARDs according to recommendations and are assessed every 3 to 6 months having their treatment adjusted as needed to achieve 3v Remission. Impact is also regularly assessed through PESS, the target being a level of "good" or "excellent". If this is not achieved despite disease activity being brought into remission or low disease activity, impact should be assessed by a more discriminating tool, such as the RAID.7 to inform the selection of the most appropriate adjunctive interventions to address the unabated domains. The process is supported by two main pillars: A. Patient Education and promotion of Self Management, and B. Shared Decision Making.

4V definition with PhGA or the adaptations of SDAI or CDAI without PGA. The advantages and drawbacks of each of these options remain to be established.

From the start, the impact would be regularly assessed through PESS. This is expected to improve progressively as the disease activity is brought under control. In case the patients still report a PESS at a level of acceptable or worse after achieving remission or LDA, the impact should be evaluated by a more discriminating tool, such as the RAID.7. Appropriate adjunctive interventions should be considered to address the unabated domains of impact, such as reinforced analgesics, antidepressants, physiotherapy or psychotherapy [63].

Individualized, personally relevant and feasible goals may be established between the patient and the healthcare team and pursued consistently, with progress being regularly measured while the disease is kept in remission.

The possibility that this strategy would provide improved results from the patient's perspective and minimize the risk of overtreatment associated with the current paradigm seems self-evident and deserving of further study.

Summary

The T2T strategy has been shown to provide significantly better outcomes than routine/standard care in RA. However, adherence to the T2T principles is still limited due to several barriers related to the patient, physician, and contextual factors.

Among these barriers, issues regarding the validity of current target definitions stand out as scientific dilemmas. Remission is the consensually prescribed target, and it is defined on the basis of either Boolean criteria or composite scores of disease activity, which include swollen and tender joint counts, CRP, PGA and PhGA.

However, recent research has shown that PGA is essentially a reflection of pain, fatigue and function, whatever their origins and also of other comorbidities, such as depression or fibromyalgia. It is poorly related to inflammation, especially at low levels of disease activity. Such findings support an increasing concern with the possibility that strict adherence to the T2T principles may lead to a considerable risk of overtreatment, without providing full control of the disease impact. The observation that up to 60% of all RA patients otherwise in remission still have a PGA score >1 (PGA-near-remission), underlines the importance of this issue.

To minimize overtreatment and optimize the impact of disease, a proposal has been made that two different targets – one focused on the disease process and the other on the disease impact – should be defined and systematically pursued. PESS is proposed as a screening instrument for disease impact and RAID.7 as a tool to identify the most affected impact domains and support the selection of adjuvant interventions.

Practice points

- PGA is included in all current definitions of treatment target in RA.
- PGA is strongly related with the impact of disease and only poorly with inflammation, especially at low levels of disease activity.
- Up to 60% of all patients with RA otherwise in remission still have a PGA score >1 and as high as 10.
- A strict adherence to the current recommendations of treatment exposes these patients to two important risks: overtreatment with immunosuppressive agents and persistent unaddressed disease impact.
- The separate consideration of two different targets – disease process and disease impact – the dual-target strategy, is proposed as a solution.

Research agenda

- What is the best definition of biological target, i.e., providing the best possible assurance of good long-term structural outcomes?
- What is best definition of impact target to be used in clinical trials and in clinical practice?
- What adjunctive measures could/should be used to address the different domains of persistent impact after biological remission has been achieved?
- What is the impact of the dual-target strategy for patients, at both the short and the long term?
- How could the dual-target strategy be implemented in clinical practice (service provision)?

Source(s) of support

None.

Declaration of competing interest

None.

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