Treat-to-target: rationale and strategies

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ABSTRACT

Treatment to a target level of a variable known to be associated with bad disease outcome is a concept that has been applied for many years in several specialties. In rheumatology this has not been the case, primarily because of the complexity of measures assessing disease activity of RA and insufficient knowledge of optimal strategies. Meanhwile, however, our insights into the devastating role of active disease have expanded. In parallel, the use of composite measures of disease activity to control patients tightly and adapt therapy accordingly has provided the evidence that treating RA to a target value of low disease activity or remission conveys significant benefit. The background of the treat-to-target concept and future aspects are discussed.

Diseases usually affect well-being, which comprises physical and mental function, as well as other features of quality of life and individual expectations. Diseases often cause damage to organs or cells; if healing and regeneration do not occur this damage will lead to impairment in organ function. Acute diseases cause this sequence rapidly over hours to weeks, while chronic diseases will result in this sequence over months to years. In other words, when treatment is instituted relatively early in the course of a chronic disease, organ damage can be prevented or minimised. It is important, however, to determine the threshold leading to such event or the maximum level of a surrogate marker at which damage will not occur or will be only minimal and thus not truly harmful in the long term. Consequently, while it might appear optimal to aim for cure, most dysregulatory diseases such as hypertension, diabetes, or rheumatoid arthritis (RA) remain without "curative" therapies, but appropriate therapy usually normalises life expectancy. The therapeutic approach should aim therefore toward prevention of future damage, or normalisation or maximal improvement of organ function, if it has occurred. Major disruption of quality of life usually does not result from signs of dysregulation, such as elevated blood pressure, glucose or joint swelling, as long as these processes do not lead to organ damage.

Thus, the threshold between harm and no harm (or minimal harm, that will not affect function or quality of life expectancy importantly, and great harm that will) is a target of utmost importance in many chronic diseases – a target that treatment should aim for. Treatment-to-target, therefore, is a general strategy with widespread implications, as long as the potential harm from treatment is carefully balanced against its benefit.

As mentioned above, there are a number of examples outside the field of rheumatology , where all this is pertinent: hypertension, diabetes, atherosclerosis/hyperlipedemia and many other. If inappropriately managed, the consequences in the long run include, stroke, heart failure, myocardial infarction, peripheral vascular disease, renal failure, blindness, etc. Indeed, our colleagues from these other subspecialties have determined target values for biological markers below which organ damage will usually not occur and life expectancy is normalised. In diabetology and cardiology, thresholds for glycosylated haemoglobin ($HbA1_c$) and glucose levels, blood pressure or lipid levels have been determined at which risk is minimised and normal organ function will be preserved (1-5). Figure 1 depicts the general strategy of treating a disease to a target level of a measure related to its long-term outcome, be it a surrogate measure like HbA1c or cholesterol level, or a composite measure of disease activity like used in RA. The strategy can be reduced to a simple algorithm of measuring → adapting treatment → measuring → adapting treatment → and so forth, until the treatment target has been achieved. Thereby treatment adap-

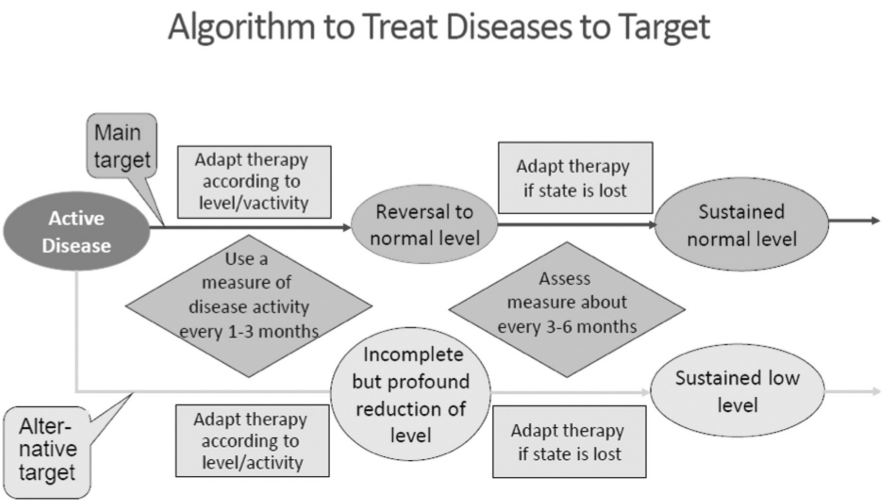

Fig. 1. Generic algorithm (after reference 4).

tation does not primarily imply changing a medication, but may relate to dose increases or even life style changes, as long as the therapeutic target is attained (or nearly attained) within a prespecified time frame. Importantly, therapeutic adaptations must take patient factors, including comorbidities, adverse events and patient preferences, into account.

Inflammatory rheumatic diseases lead to organ damage affecting the musculoskeletal system (and the systemic diseases additionally harm the internal organs). The musculoskeletal system cannot be assessed by using a simple surrogate or direct "gold standard" measures, such as available when caring for patients with diabetes, hyperlipidemia or hypertension (6). Rather, the complexity of the signs and symptoms of these diseases ("disease activity"), but partly also the knowledge which of those are associated with progression of damage, requires the application of composite scores (7-15). Likewise, "organ function" cannot be evaluated by using only a laboratory value, particularly as 40% of patients have normal CRP or ESR at presentation (16, 17), which may not change with clinical improvement. Information from phyiscal exmination using a quantitative joint count are of utmost importance (see below). Additionally, information from the history, which can be collected through patient self-report multifaceted questionnaires, has proven effective in determining patient status and its changes (18-21).

However, as with other organs, functional impairment of the musculoskeletal system has reversible and irreversible components, and the latter is mostly dependent on damage (22, 23); this relationship can even be quantified (24, 25). Since joint damage is a direct consequence of disease activity (9, 11; 26, 27) and disease activity is a major contributing factor to reversible impairment of physical function (22, 28) The most important variables contributing to joint damage are swollen joint counts and C-reactive protein (9-11, 26). It is this compelling evidence which make the use of composite measures of disease activity that comprise joint counts so important. Thus, reducing disease activity as assessed by such composite measures will improve physical function and retard progression of joint damage. Moreover, significant joint damage will not only lead to irreversible disability, but at some point impairment of physical function may not improve with active medication beyond a placebo effect (29). This is the limitation of focussing too much on patient reported outcomes for disease activity assessment.

To determine optimal treatment targets in RA, however, it is necessary to define the thresholds of disease activity measures at which progression of joint destruction is halted and improvement of functional impairment maximised. Indeed, cutpoints between high, moderate, low disease activity and remission have been defined for the major composite scores (30, 31). Only remission is associated with maximal reversal of functional impairment and a stop of progression of damage (32, 33) as well as work disability (34); however, some remission criteria are more stringent in this respect than others, and, therefore, new criteria have recently been defined by ACR and EULAR (35).

While not the optimal state, low disease activity also dramatically retards damage accrual and improves physical function when compared with moderate and high disease activity (32, 33); it is, therefore, likewise an acceptable treatment goal, especially in established disease. This conclusion relates primarily to treatment with methotrexate. While combination therapy of a biological agent with MTX will inhibit joint damage irrespective of disease activity (30-38), irrespective of the type of therapy, impairment of physical function will increase with higher disease activity states (39). Thus, if a therapeutic target that relates to optimal outcome is to be chosen and can be relatively easily attained, then it should be remission; an alternative target, at which accrual of joint damage and disability is significantly reduced would be low disease activity.

It has been shown in several trials that targeting low disease activity by regular monitoring using primarily composite measures of disease activity and adhering to a predefined treatment strategy, when compared with unstructured treatment, conveys better outcomes (40-44). In the TICORA trial, for example, there was significant clinical and radiological benefit in favour of the strategic treatment group; however there was still significant damage progression even in this population of patients, presumably because low disease activity rather than remission was targeted (40). Moreover, in this and other strategic trials (45, 46) high response rates were achieved upon DMARD plus glucocorticoid use even without employing biological agents, showing that strategy is more important than particular agents and that biologics should be reserved for patients who do not respond to traditional DMARDs plus glucocorticoids and have active disease or other risk factors for bad outcome, as suggested in the EULAR management recommendations (47).

Before realisation of the benefit of tight control and according treatment adaptation, it had been recognised that initiation of DMARD therapy early in the disease course provides significant benefit in terms of damage and function over delays of starting treatment (48-50). Early therapy requires early diagnosis which depends on early referral and criteria that allow recognition of early disease. Such referral recommendations, ways to cope with the evaluation of patients who visit clinics early and new classification criteria for RA have, indeed, been recently published (51-53).

To account for all the information accrued over time, namely (i) RA characteristics that relate to bad outcome; (ii) determination of best and second best outcomes in RA; (iii) optimal criteria for the definition of these good outcomes; and (iv) optimal treatment strategies, an international task force has developed recommendations for treating RA to target ("T2T") (54). These recommendations, which were based on a systematic literature review and intensive group discussions (44), comprise four overarching principles and 10 recommendations, which essentially summarise the state of art evaluating RA and treating RA in terms of therapeutic strategy, complemented by the pivotal aspect of patient involvement into all decision making.

The T2T recommendations suggest adapting therapy if there is no improvement within 3 months from its start or if the treatment target, which is defined as remission in early RA and at least low disease activity in established RA, is not attained within 6 months. While it was discussed at length whether the composite measure used should or should not include joint counts, it was decided by a very large that majority measures which include joint counts should be employed, because joint swelling has for long and consistently been found associated with progression of joint damage (9, 11, 26, 55). Moreover, these composite scores correlate well with physical function at all disease stages (27) and allow one to use physical function as an additional outcome (55, 57).

Importantly, the T2T recommendations do not deal with any particular type of drug or groups of agents and, to this end, are generic, since an optimal outcome should be sought irrespective of the availability of specific drugs. (Approaches to using specific drugs for treating RA have been provided by ACR and EULAR (47, 58))

An anonymous survey on the agreement with the T2T recommendations involving over 1500 rheumatologists revealed a very high level of agreement with every item, achieving more than a mean of 8.4 points on a 0–10 point scale (59). However, such agreement does not necessarily mean that these physicians also have implemented the recommendations in their practice. Indeed, one of the limitations of such recommendations relates to the inability to control for their use. Therefore it will have to be seen in the near future if the overall outcome of RA will improve and future patient surveys may allow one to learn if DMARDs are switched more frequently than before with continuing active disease.

To account for patient involvement, patients must understand the value of such recommendations. To this end, a group of patients and rheumatologists came together to adapt the language of the recommendations to patients' needs (60). This may allow better involvement of the patients into the discussions with their doctors and their care. Indeed, several items of the T2T recommendations address the necessity of a shared decision making and, as discussed above, treatment-to-target is a principle embedded within the patient context and not, *per se*, an untouchable decree. Special care must be taken as to avoid misinterpretation of the recommendations: while remission is an ideal goal, many patients, especialy those with longer standing disease, may not be able to reach remission and patients as well as physicians caring for them should be sometimes satisfied if the alternative of low disease activity, or even a status close to that alternative, is attained, rather than pushing to achieve a status that may not be achievable.

In particular, as also addressed in the T2T recommendations, comorbities must be taken into account; patients with RA are afflicted with a variety of comorbidities (61) and comorbidities affect physical function over and beyond the disease itself (28, 62). Just as many other recommendations, the T2T recommendations for RA point to an ideal treatment goal, but also provide an alternative to this ideal state and address additional factors that have to be borne in mind (54).

As with every set of recommendations there are barriers regarding their application in practice. In many discussions worldwide it turned out that performing joint counts is an obstacle because of time or resource constraints. This will have to be overcome with implementation programmes and supportive measures, since it is difficult to understand how rheumatologists can neglect the organ they are caring for, the joint.

Recommendations developed at a particular point in time require revisiting at regular intervals, since new insights may have developed. Moreover, a research agenda had been proposed in the context of the T2T recommendations. Therefore, the T2T recommendations for RA will be reassessed in the near future by performing a new literature search looking out particularly for answers to items of the research agenda developed in the course of the deliberations on the individual recommendations. Furthermore, the question arises if T2T has value only for RA or could not be also applied in other chronic inflammatory rheumatic diseases – this is currently developing for spondyloarthritis and other diseases, as discussed elsewhere in this supplement.

Thus, the T2T concept may become widely applicable and used in clinical practice and it is hoped that this will ultimately provide significant benefit to our patients.

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