Treat to target: a winner strategy in rheumatology. From the past to the future

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Introduction

Treat to target (T2T) strategy was defined in 2010 in rheumatology, when international expert committee developed recommendations to achieve the best therapeutic outcome in rheumatoid arthritis (RA).[1] Until then, clinical outcome in real life imitated clinical trials endpoints, using surrogate outcome measures or instead using clinician's impression. The recommendations to achieve remission as primary goal or low disease activity defined the dynamicity of therapeutic strategies to reach established target with defined outcome measures. This treat to target approach has been evaluated by a clinical trial in 2004, the TICORA study, with implementation of frequent visits protocol with step-up therapeutic strategy, starting with sulfasalazine up to combo-therapy with methotrexate.[2]

To this day T2T strategy, in rheumatoid arthritis field, is still studied and up for discussion, especially regarding the utility of validates measures of disease activity, both clinical and instrumental (*i.e.*, ultrasound or MRI).[3]

However, the initiative of international task force was fundamental to the rheumatological therapeutic scenery as well as the consequences derived from these recommendations about the timing of visit or the goal to reach in every patient.

Beyond RA, T2T approach was used to manage many chronic diseases, such as hypertension, dyslipidemia, and diabetes, showing to be able to improve the outcome of these diseases.

In this context, T2T strategy had been developed in rheumatology also in other rheumatic disease.[4]

Rheumatoid arthritis

The appearance of biological drugs has changed the way of thinking about the goals to be achieved in patients suffering from RA, allowing the possibility of sustained remission or an arrest of the progression of structural damage or disability.[5] The aim of remission must be pursued in most patients, while low disease activity can be achieved in patients with long-standing disease. As measure of target ought to be a composite indices of disease activity, as a good predictor of articular damage and disability. T2T recommendations since 2010 proposed DAS28, CDAI/SDAI as measures, if composed by clinical evaluation, laboratories value and patient assessment. Moreover, structural changes and functional impairment should be evaluated in clinical decision, but they should always be shared with patient.[1]

In achieving remission/LDA, clinical evaluation (joints count) is essential. The strategy of using imaging methods to detect subclinical disease activity, unrecognized, is debated: the use of MRI is unfortunately unfavorable cost effectiveness, while ultrasound, more favorable cost effective, still offers mixed results.[6-9]

Spondyloarthritis/psoriatic arthritis

In 2014, Smolen *et al.*[10] as International Task Force, elaborated the recommendation to treat to target spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, subsequently updated in 2019,[11] with the primary goal of reducing symptoms, inflammation, and structural damage. Unlike rheumatoid arthritis, in SPA recommendations include direction about extraarticular manifestations of SpA as potential therapeutic targets and suggest imaging technique as an adjunctive kind of assessment for disease activity. In fact, all imaging methods (X-ray, CT, MRI and US) were included in the evaluation, although no score or preferred site preference was indicated.

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The SPA guidelines, as used in rheumatoid arthritis, are originated from two clinical trials, TICOPA[12] in psoriatic arthritis published in 2015 and TICOSPA[13] in spondyloarthritis, recently published, but started in 2016.

While in PsA the target indicated is the achievement of minimal disease activity, in SPA the ASDAS score is recommended for inactive disease/remission o low disease activity. Although spinal or Sacroiliac joint's inflammation detected through MRI was associated with disease activity both by ASDAS or BASDAI, if MRI would be a target of therapies requires further studies.[14,15]

Another difference between RA tight control studies' and spondyloarthritis is therapeutic approach, because in TICOPA and TICOSPA biologic therapies (TNF inhibitors) were used as part of step-up strategy, while in TICORA were not.

Ultimately, in 2019 update of SPA guidelines, the panel does not recommend the treat to target approach in spondyloarthritis for a lack of direct evidence of association between lower disease activity and lower radiographical progression, and because of the too-high costs of T2T strategy.[16]

Systemic lupus erythematosus

Despite the introduction of some new target therapies and the evidence of their efficacy, in systemic lupus erythematosus (SLE), morbidity and mortality remain unsatisfactorily high, thus more interest is required to improve treatment strategies for these patients. An international experts' panel on T2T in SLE published recommendations[17] emphasizing multidisciplinary care, prevention of organ damage and flares and reducing the mortality. Although defining an outcome as effective or a targeted therapy is challenging, the lupus low disease activity state or remission in SLE proposed by experts is still a matter of debated today.[18-20] It must be considered that the set of organ damage and glucocorticoids adverse effects may be mistake clinical evaluation of disease activity.

Gout

Treating to target the gout is established on to prevent crystallization of monosodium urate and crystal deposition in joints, through lowering serum urate levels. This is a fundamental principle of gout management.

The serum urate level under 6 mg/dL is defined as the most effective treat to target goal by major rheumatology societies recommendation and guidelines.[21-23] Although there is not strong evidence to demonstrate efficacy of T2T strategy in gout, there are indirect evidence that it is clinically effective in daily practice, as well as supports this approach also clinical open label extension and post hoc analysis of clinical trials.[24]

Osteoarthritis

For many rheumatic diseases are available biomarkers, outcome measures and instrumental evaluation for stadiation or activity disease, like the possibility of early diagnosis. These indexes allow to formulate diagnostic algorithm, therapeutic strategy and treat to target purpose for many of them. Moreover, the availability of therapeutic choices among different drugs and in some cases, even with different mechanisms of action, leads to the need to put in order and classify the patient for the most appropriate choice. These are only partially available for osteoarthritis (OA).

OA is a disease with several phenotypes (inflammatory, mechanical, genetic, metabolic, *etc.*)[25] but since only a few drugs and not outlined non-pharmacological intervention are available to halt disease progression, it is impossible to propose the same strategy for every phenotype of OA and/or involved joint.

European League Against Rheumatism (EULAR) try to delineate strategy of intervention for hip and knee osteoarthritis, principally about non-pharmacological treatment[26] suggesting some topics as patient information and education, lifestyle changes and weight loss, exercise and work-ability.

Most recently, Osteoarthritis Research Society International (OARSI), published in 2019, guidelines for non-surgical treatment of knee, hip and polyarticular osteoarthritis,[27] with recommendations about three pharmacological lines of treatment and an algorithm patient-based to program follow-up and decision-making process.

Contextually, in the same year, an international technical expert panel (TEP) published the consensus and the treat to target strategy for knee OA,[28] starting from clinical definition of primary treatment target through the Patient Acceptable Symptom State (PASS) on pain, patient global assessment and functional improvements.[29] Their good clinical practice statements are based on early symptomatic diagnosis and treatment (pharmacological, non-pharmacological and lifestyle), dynamic tight control patient-customized (every 3-6 months), documenting measures of clinical improvement, safety and efficacy regularly (suggesting Likert scale, WOMAC, VAS-Pain, HAQ), with periodic follow up discussion about comorbidities and modifying progression risk factors. The TEP also proposed the most innovative T2T strategy statement to adapt treatment according to patient phenotype and disease severity, pointing out the heterogeneity of pathogenetic and clinical progression of manifestation, as previous reported by a systematic review of literature.[30]

Treat to target: a look to the future

An implementation of T2T strategy would provide extension of use of clinical guideline and recommendation disease-specific in every clinical setting, but also it would assure ease of access to treatment, reducing waiting times and the bureaucratic burden of the rheumatologist specialist. Instrumental implementation during visits as ultrasound (musculoskeletal, salivary glands, large vessels or lungs) and capillaroscopy may add more precision and specific information in stadiation activity disease or follow up.

Technological tools could improve the quality of care, reducing the distance between the doctor and the patient, allowing a better and tighter control and participation in patient reported outcomes. Mobile devices (smartphones, wearables, and tablets) through dedicated apps, would provide the right support

to healthcare professionals and patients, tracing the daily symptoms and sharing therapeutic information, clearly not as a substitute of medical examinations.

Ultimately, the correct application of the treat to target strategy starts by educating patients in doing primary prevention to have early diagnosis, also through informative campaigns for the population and through the support of scientific societies towards payers, to help them in the management of human and economic resources to treat patients well and better.

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