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EDITORIAL

Therapy protocols – Past, present and future

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Abstract
Since autoimmune rheumatic diseases comprise a large variety of diseases, with different types of manifestations, there is a real need for a well defined treatment strategy. This comprises, among others, the window of therapeutic opportunity concept and the treat-to-target strategy. Once these elements are in place, there is another need for conceiving therapeutic protocols, usually on a national level, that combine the medical information contained in specific guidelines as well as the economic constraints of each health system. This paper aims at reviewing these key concepts and the some of the national therapeutic protocols concerning the most common autoimmune rheumatic diseases.
Keywords: autoimmune rheumatic diseases, treat-to-target, biologic DMARD, targeted synthetic DMARD.

Introduction

Autoimmune diseases encompass a variety of pathologies, from those affecting a single organ, for example Hashimoto's disease, also known as chronic lymphocytic thyroiditis, to systemic diseases. Autoimmune rheumatic diseases affect mainly, but not exclusively, joints and the muscular system. These pathologies include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), axial spondylarthritis (AS), psoriatic arthritis (PsA), systemic sclerosis (SSc), Sjogren's syndrome, idiopathic inflammatory myopathies and vasculitis. Systemic autoimmune diseases are defined by heterogenous clinical aspects and lab oratory findings, and a significant morbidity and mortality [1].

Previously, therapeutic options for treating rheumatic autoimmune diseases were limited to non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids. Eventually, the treatment arsenal was extended to conventional synthetic disease modifying drugs (csDMARDs), such as methotrexate, sulfasalazine, hydroxychloroquine, each with their particular set of specific indications and adverse effects. These therapeutic agents play an essential part in the treatment of rheumatic diseases. The defining moment in therapeutic strategies in rheumatology occured at the end of the twentieth century with the introductions of biologic disease-modifying drugs. These monoclonal antibodies target specific molecules that were key elements in the inflammatory process. Presently, biologic treatment has expanded to multiple classes of diverse molecules, but also targeted synthetic treatment. Each of these therapies have a different molecular target and entails specific monitoring regimes and safety profiles [2].

Considering these aspects and the need for individualized treatments to optimize the therapeutic potential of each molecule, it is crucial to establish and implement guidelines and protocols. These protocols represent a set of regulations established at a national level and are provided by a group of experts. The foundation of all protocols is represented by randomized clinical studies, international guidelines and treatment algorithms. Protocols allow a harmonization and standardization of therapeutic strategy and, ideally, ensure avoidance of under- and overtreatment. Therapy protocols are periodically reevaluated in order to provide an optimal management of pathologies. These sets of regulations must encompass mandatory elements such as therapeutic indications, inclusion and exclusion criteria, contraindications, precautions and treatment monitoring strategies. Currently in clinical practice, the goal is to attain an optimal management strategy, to maximize treatment efficacy and reduce adverse effects. This strategy is presently based on several therapeutic principles. The most significant are represented by the "window of opportunity" and the "treat-to-target" (T2T) strategy [3].

Window of opportunity

The prognostic of patients with RA has changed significantly over the past 25 years. This is a result of

the development and use of DMARDs, application of personalized strategies that enhance disease control, and an earlier initiation of targeted treatment. Starting treatment in an early stage of disease allows a better control of the pathogenic process and the potential to reverse structural damage. This stage has been named the "window of therapeutic opportunity". It has been established that early implementation of treatment may lead to reduced radiographic joint damage and lower progression rates. The current perspective regards the window of opportunity as part of the phase of the disease that precedes an established diagnosis, in which initiating treatment may prevent the manifestation of RA [4]. On the other hand, RA is a systemic disease, defined by the presence of multiple extra-musculoskeletal manifestations with a significant impact on prognosis. One of the most important RA-associated disorders, both because of its high prevalence, reduced quality of life of patients and increased mortality, is interstitial lung disease (ILD). The window of opportunity may be a valid concept not just in regards to joint involvement, but also in order to prevent lung fibrosis. The current objective is to evaluate ILD progression to establish a highly efficient management plan for these patients [5]. A window of opportunity has not yet been demonstrated in other autoimmune rheumatic diseases, such as SLE. Furthermore, the definition of early disease has yet to be elaborated. One of the challenges concerning this aspect is the implementation of efficient strategies, to reach an early diagnosis. These elements will be essential when a window of opportunity period will be determined. This will imply demonstrating its significance regarding lowering mortality rates, disease activity and effects on Health-Related Quality of Life (HRQoL) [6].

Treat-to-target

The treatment objective is represented by the limitation and control of disease activity, taking into account that high levels of disease activity lead to a greater risk of joint damage and mortality. A defining element of this proactive strategy, „treat-to-target", is the frequent and systematic evaluation of disease activity through validated methods, and comparison with a set target, established before treatment initiation. If the target is not reached within a designated time frame, the treatment is escalated [7]. This principle has proven efficient in multiple medical areas, such as arterial hypertension therapy [8]. In RA, the goal is based on a composite index, for example Disease Activity Score (DAS), with the assessment of 28 joints, the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Score (CDAI). The manner in which this principle is implemented seems to vary on a national or regional level. These differences are often due to regulations of an administrative and economical nature, more so than because of results of clinical studies. International guidelines identify disease remission as a therapeutic target for newly diagnosed RA. For an established disease, low disease activity (LDA) is also accepted [9].

Although there is limited proof regarding the direct long-term benefits of T2T in spondylarthritis, this strategy has been recommended for implementation in this group of diseases in 2014 [10]. This recommendation is based on the indirect effects of inhibiting the inflammatory process in axial Spondylarthritis (AxSpA) and a better disease activity control, which prevents structural damage and functional disability. There are challenges regarding the designation of an optimal target, given the disease heterogenicity. This implies axial involvement, the possibility of peripheral joint manifestations, but also extra-musculoskeletal disease [11]. The treatment objective, as in RA, is represented by disease remission/inactive disease. Clinical remission is defined by the absence of disease activity following clinical examination (arthritis, dactylitis, enthesitis, axial involvement), but also normal inflammatory markers (erythrocyte sedimentation rate, C reactive protein). Once remission is attained, this status must be maintained over time. Disease activity assessment should be done on a 6-month basis or more frequently in patients with high disease activity (every one to three months) [12].

SLE is a complex and highly heterogenous disease defined by a multitude of clinical manifestations and an undulating progression. Thus, SLE disease activity is assessed using a variety of composite indexes and, as such, the objectives are multiple. They are represented by disease activity control, lowering the systemic glucocorticoids dosage and preventing damage accrual of different organs and systems [13].

Why do we need treatment protocols?

Given the destructive potential of rheumatic diseases, with severe joint damage but also systemic manifestations, early therapeutic intervention is essential in reducing disease impact on the quality of life of patients. Treatment objectives are represented by attaining disease remission or LDA. Achieveing these targets is the definite way to prevent joint destruction and improve quality of life. Failure to attain the therapeutic target in a time frame of 6 months, in which the patient has adhered to treatment according to the set guidelines, justifies the need to add a biologic DMARD (bDMARD) or a targeted sintetic DMARDS (tsDMARD) to the therapeutic regimen. Some of the leading causes regarding different types of medical decisions in clinical practice are the reluctance to adopt novel therapies, the lack of studies or difference in reimbursement of various diagnostic tests. These diferences in clinical decisions may have consequences of an economical type or related to treatment efficacy. Healthcare professionals that adhere to using only classic treatment options can limit the favourable clinical progression of patients. On the other hand, reaching for novel therapeutic agents for all patients may lead to a cost growth in the

medical system, without a proven higher general efficacy. Thus, one essential argument for the need to adopt a treatment protocol is facilitating the medical decision [14].

Pros and Cons

Protocols assure the rentability of these therapeutic agents, taking into account the clinical profile of each patient and the severity of the disease. This system has enabled a restriction of the most efficient therapies (biologic treatment, targeted synthetic agents), justifying their use only in patients with severe disease (high activity), that had no response to the standard treatment. This limitation has rendered moderate disease activity as acceptable. The impact of a disease with moderate activity on pain, mobility and quality of life can be major and these patients present various unmeet needs regarding their treatment [15]. Clinical studies have highlighted a prompt response to therapy of patients with moderate disease activity and a higher probability of reaching and mantaining remission [16]. This leads to advantages such as better employment options, keeping the current workplace and reducing long term necessity of orthopedic interventions [17]. Another disadvantage of therapeutic protocols is represented by the atypical patient. By definition, clinical studies that are the basis of guidelines take into account efficacy and adverse effects as observed on a selected patient group. Subgroup analysis that could explain the difference in response rates may not be adequate due to low patient numbers, while information regarding responders and non-responders may be scarce. Protocols based on this type of data denote a general similarity in disease activity, response to treatment and adverse effects risk. Therapeutic agents that have shown efficacy in a group of patients may not have the same results or may be inadequate for other patients. Thus, protocols do not emphasize the individual variation of patients [14].

Different national protocols and guidelines

GUIPCAR, the national guideline of the Spanish Society of Rheumatology for patients with RA, recommends using b/tsDMARDs in association with a csDMARDs in patients who lacked a treatment response to two previous csDMARD therapies. Current spanish recommendations support using a csDMARD as initial therapy, with methotrexate being the treatment of choice. In case of a inadequate response to methotrexate, other csDMARDs can be used. The presence of negative prognostic factors facilitates the initiation of bDMARDs therapy. The Spanish Society of Rheumatology justifies this recommendation through multiple clinical studies. They underline the current strategy of early treatment initiation, in order to benefit from the „window of opportunity" and T2T [18].

In France, access to biologic treatment is high, with a short mandatory period of csDMARD therapy. In RA, in case of intolerance or inefficacy of methotrexate, patients with negative prognostic factors may start treatment with b/tsDMARDs [19]. In 2019, in Singapore, after a reevaluation of the inclusion criteria for biologic therapy in RA, moderate disease activity according to DAS28 was deemed appropriate for intensifying treatment and escalate to bDMARDs [20].

Previous recommendations of the National Institute for Health and Care Excellence (NICE) from the United Kingdom stated that, in RA, bDMARDs could only be administered in patients with high disease activity and no response to csDMARDs in combination therapy [21,22]. In order to control disease activity, long term treatment with systemic glucocorticoids may reduce the activity score, however it poses a high risk for certain complications, such as osteoporosis. Adding glucocorticoids to the treatment strategy in patients with RA and moderate disease activity has been a frequent practice in the UK, as a consequence of the restriction to advanced therapies imposed by the NICE guidelines [23]. Using novel solutions for such challenges is essential. There is a need to implement optimal strategies for the identification of patients that may benefit the most from biologic therapy. Multiple associations founded by patients diagnosed with autoimmune rheumatic diseases have reviewed the evidence regarding the benefits of early implementation of advanced therapies in patients with moderately active RA. Thus, the active role of patients in treatment decisions may have positive effects on a grand scale [24]. The introduction of biosimilars as a therapeutic option has lowered the costs of bDMARDs treatment, demonstrating a similar efficacy in RA management. Thus, data has shown that the development of the etanercept biosimilar has had a significant effect in lowering average treatment costs in rheumatology [25]. Recently, in the UK, guideline changes have led to the possibility to initiate b/tsDMARDs treatment in moderately active RA. It has been estimated that approximately 25000 such patients have now become eligible for advanced therapy [26]. Unlike the UK, in other European countries, particularly Northern Europe, and in the United States of America, nominating moderate disease activity as inclusion criteria for b/tsDMARD treatment has been previously achieved. The European League Against Rheumatism (EULAR) has elaborated clear recommendations regarding administering biologic agents to patients with negative prognosis factors, non-responders to methotrexate therapy. As a direct effect of biosimilars and reduction of treatment costs, a higher number of patients are now benefiting from advanced therapy worldwide [27].

Clinical studies

A clinical study published in 2022 in Norway underlined a reduction of the annual treatment costs of approximately 75% in biologic naïve RA patients between the years 2010 and 2019. The percentage of RA patients treated with ts/bDMARDs increased from

39% in 2010 to 45% in 2019. The percentage of patients that were in remission improved from 42% in 2010 to 67% in 2019 [28]. In the multicentric NOR-DMARD study, it was emphasized that remission rates after treatment with tumor necrosis factor inhibitors (TNFi) increased from 17% in the years 2000-2002 to 46% in 2009-2010. One of the main reasons for differences in overall treatment costs reduction is the transition, with the patient's approval, to biosimilars but also the availability of biologic treatment at a lower cost [29]. In 2009, in Romania, an estimated 2.2% of RA patients were receiving bDMARD treatment, with an increase to 9.6% in 2013 [30].

In the search to standardize the management plan of such heterogenous diseases, clinical studies have compared various national treatment protocols and guidelines. The main points of interest in the conduction of this comparison were as follows: the level of similarity and potential major differences between protocols, the impact of these guidelines in clinical practice and the assessment of the type of protocol that may be needed in the future. A systematic review conducted in 2019 analyzed 22 RA protocols and management guidelines. The main objective of this review was to emphasize the major common points but also the differences of these protocols. The features that were found in the great majority of the guidelines were: 1. DMARD treatment should be initiated as early as possible after diagnosis, 2. Disease activity must be periodically evaluated, using composite indexes, such as DAS28, 3. Methotrexate is considered a first line medication and can be used in association with systemic glucocorticoids, the latter as "bridge therapy", 4. bDMARDs should be started in patients with persistent active disease that were administered methotrexate, and in some protocols, a second csDMARD, 5. Adequate treatment targets are represented by disease remission and LDA, and in patients with sustained remission tapering of ts/bDMARD dosage can be considered [31].

Other medical specialties

Besides rheumatology, management protocols have been elaborated for a variety of clinical specialties, for example dermatology, gastroenterology, oncology, endocrinology, cardiology, nephrology and infectious diseases. Among the first treatment protocols were those regarding chemotherapy regimens. These protocols had elaborated the steps that needed to be taken before administering chemotherapy, during treatment and also after delivering the therapeutic agent. Frequency of laboratory testing, vital functions monitoring, dosage and intravenous administering rates were some of the main points of focus of these regulations. Many specialties could benefit from implementing well-defined national protocols, in order to increase the quality of healthcare and reduce treatment-related costs in the health system. This can be supported by highlighting the optimal management plans according to clinical studies, enabling proficiency of the medical decision (14).

Conclusion

National treatment protocols must aid patients in receiving quality healthcare and provide means to lessen the burden of disease. Personalized treatment and efficient selection of eligible patients for treatment with ts/bDMARDs may lead to an increase in the quality of life of patients and a reduction in the economic impact of autoimmune rheumatic diseases. Presently, most clinical studies that refer to the "window of opportunity" are conducted on patients with RA. This can be considered a stepping stone for developing such principles in other pathologies, especially SLE and spondyloarthritis, where efforts have been made to accomplish this feat. The main objectives are the individualization of treatment, the diversification of therapeutic options and a greater access to treatment in order to reduce the negative impact of these complex pathologies.

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