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Current Status and Future Challenges in the Treatment of Rheumatic Diseases

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INTRODUCTION

In the last decades, the treatment of rheumatic diseases has been revolutionized by a deeper understanding of their physiopathology, the introduction of several new treatments with different targets, and the comprehension of the importance of a strategic approach to these diseases.

STRATEGIC APPROACH TO TREATMENT

The strategic approach is probably as important as the incorporation of new drugs and their new mechanism of action. The strategic approach to rheumatic disease includes early diagnosis and early treatment, remission as the main objective of treatment, frequent assessment of disease activity using validated measurements tools, adjustment of treatment when the objective is not achieved (called treat to target strategy), and finally, shared therapeutic decisions with the patients. Each one of these strategic points are not only intuitively appealing, but also based on good evidence.

Early Diagnosis and Treatment

That early diagnosis is associated with better long-term outcomes has been proved for rheumatoid arthritis (RA) (Aletaha and Smolen, 2018), psoriatic arthritis (PsA) (Tillett et al., 2013), spondyloarthritis (SpA) (Barnett et al., 2020), systemic lupus erythematosus (SLE) (Sebastiani et al., 2016), systemic sclerosis (SSc) (Minier et al., 2014), and antiphospholipid syndrome (APS) (Tektonidou et al., 2019), to mention some. To achieve early diagnosis and treatment of rheumatic diseases are the objectives of many efforts in the rheumatology community.

Remission as Treatment Goal

To aim for remission as a treatment target has been stressed by multiple recommendations in different diseases such as RA (Smolen et al., 2020), PsA (Coates et al., 2014; Gossec et al., 2020), SpA (van der Heijde et al., 2017), SLE (Pons-Estel et al., 2018), etc., although the definition of remission has been elusive for some multidimensional diseases such as SLE (Aringer et al., 2019) and PsA (Acosta Felquer et al., 2014; Soriano, 2015). Nowadays almost all rheumatologists are aiming for remission when treating their patients and share this objective with their patients.

Treat to Target

The concept of treat to target has evolved over time for different rheumatic diseases (Smolen, 2019). The treat to target strategy has been well proved by randomized clinical trials only in a few diseases such as RA (Salomon-Escoto and Kay, 2019) and PsA (Coates and Helliwell, 2015), has been challenged in others such as SpA (Molto et al., 2021), and has indirect evidence in SLE (Aringer et al., 2019) gout (Perez-Ruiz and Dalbeth, 2019), and inflammatory myopathies (Vencovsky et al., 2019).

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In any case, the basic principles on which the strategy is built stand for all these diseases. Those principles are the use of measures that allow the assessment of disease activity and that correlate with disease progression and physical function; and the availability of effective treatments able to induce remission which in turn will influence damage progression and provide dramatic advantages in outcomes (Smolen, 2019). Without good measurement tools of disease activity and effective treatments capable to achieve the goal of remission, the treat to target strategy is simply not possible.

Shared Therapeutic Decisions

It has been shown that less patient participation in clinical decisions is associated with less satisfaction with the decision process (Nota et al., 2014). Low patient satisfaction on the other hand is associated with poorer outcomes and lower adherence to therapy (Anghel et al., 2018). Despite this knowledge, there is still a lot of medical education needed to achieve ideal levels of shared therapeutic decisions in daily clinical practice (Mathijssen et al., 2020).

CURRENT CHALLENGES FOR RHEUMATOLOGISTS

Drug Safety

Rheumatologists have been lucky in the last decades because there has been enormous resource investment into the development of new drugs with many different mechanisms of action. This resulted in huge changes in the outcomes and quality of life of patients. The mandatory study design for the approval of new drugs is the randomized clinical trial (RCT). Some of the limitations of RCTs are their short duration (3–5 years) that does not give correct estimates of the lifetime effects of the interventions, and the inclusion of highly selected patients that are not representative of real-world populations (Kostis and Dobrzynski, 2020). This raises the question of what the effectiveness of this treatment in real life would be, and of utmost importance, what will be the long-term and generalizable safety of the developed drug?

To have safe drugs for the treatment of rheumatic diseases is one of the current challenges of this specialty and one of the major concerns of patients. People's perceptions of their medications and their safety heavily influence adherence and drug persistence (Anghel et al., 2018).

Drug surveillance and real-life data are of extreme importance if some infrequent adverse events are going to be detected. There are a good number of examples where adverse events in drugs only clearly appeared once the medication was approved and used in real life. The association of tumor necrosis factor alpha inhibitors (TNFi) with tuberculosis was not detected during clinical trials, but only reported after these drugs were approved and used in real life in patients with Crohn's disease and rheumatoid arthritis (Keane et al., 2001). The increased risk of lower gastrointestinal perforation in patients with rheumatoid arthritis treated with tocilizumab, although seen during clinical trials (Schiff et al., 2011), was only more clearly reported after approval and with observational studies (Gout et al., 2011). Very recently, data emerged from observational and randomized clinical trials related to increased lipids levels and cardiovascular risk and thrombosis in patients with rheumatoid arthritis treated with Janus kinases inhibitors (JAKi) (van der Heijde et al., 2019).

In fact, based on the results of a 4-year randomized, open-label, noninferiority, post authorization, safety end-point trial, in which patients with active rheumatoid arthritis despite methotrexate received tofacitinib twice daily or a subcutaneous tumor necrosis factor (TNF) inhibitor (etanercept or adalimumab) (Kremer et al., 2021), the Food and Drug Administration (FDA) in the US issued a black-box warning for JAK inhibitors and changed the indications for tofacitinib and upadacitinib from incomplete response to methotrexate to incomplete response to a TNF inhibitor.

Several long-term follow-up studies, surveillance studies, and real-world data have not found an increased risk of cardiovascular events and cancer in patients with rheumatoid arthritis treated with JAK inhibitors, but usually these studies lack a control group (Charles-Schoeman et al., 2016; Cohen et al., 2020; Mease et al., 2020).

Safety issues and safety concerns and their relationship with regulatory agencies are far from solved, and would need much more research and publications, for which dedicated journals are welcomed.

Precision Medicine

Despite the many advances made in the past three decades on the knowledge of the pathogenesis of many rheumatic diseases and the identification of several novel therapeutic targets and treatments, we have been unable to identify which treatment will be of more benefit for each patient, and in most cases, treatment recommendations are based on a trial-and-error approach.

Predicting which treatment will be efficacious for an individual patient or disease domain involvement would be extremely valuable both for patients and physicians.

However this does not mean the creation of a drug or medical device that is unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their response to a specific treatment, as stated by the National Research Council of the US National Academies FDA, (2011).

Some genetic, serum-soluble, cellular, and tissue biomarkers have been identified that help better classify subpopulations in different rheumatic diseases and might predict treatment response in many of them, however those findings have not yet been implemented in daily clinical practice (Demirkaya et al., 2019; Jadon et al., 2020; Wampler Muskardin et al., 2020). More clear and easy approaches are needed. For example, in rheumatoid arthritis with the exception of a few clinical situations (Poddubnyy, 2021) (e.g., superiority of tocilizumab compared with adalimumab—a TNF inhibitor—in patients requiring monotherapy (Gabay et al., 2013); somewhat better response to abatacept compared with adalimumab in patients with poor prognostic factors, including a high concentration of anticitrullinated protein antibodies (Fleischmann et al., 2019);

and an overall better response to rituximab in patients who are seropositive compared with patients who have seronegative rheumatoid arthritis (Courvoisier et al., 2021)), there are currently no markers that could be used for a precision medicine approach in clinical practice.

There is also some rationality on the theory that response to a specific drug could be related to the molecular pathway targeted by the drug in the synovium. Using this theoretical framework, the findings of studies linking response to therapy with synovial changes provide promising perspectives on bridging the gap to precision medicine in RA (Triaille and Lauwerys, 2019). However as synovial biopsy is an invasive procedure, the information gain should justify its use in clinical practice (Poddubnyy, 2021).

In psoriatic arthritis, a single group reported good predictive response to therapy using phenotyping of peripheral blood lymphocytes by flow cytometry through the identification of intracellular signals, and classified psoriatic arthritis patients in four groups based on the lymphocyte phenotypes found (Miyagawa and Tanaka, 2020). However, the technique is not available in clinical practice and features need to be validated with a larger number of patients and by other research groups.

In lupus, high levels of type I interferon (IFN), that presented in 50% of patients, have been associated with several genetic factors and with cutaneous and renal manifestations and the presence of autoantibodies, such as anti-Ro, anti-Smith (anti-Sm), anti-RNP, and anti-dsDNA antibodies (Wampler Muskardin et al., 2020). Clinical trials of monoclonal antibodies targeting type I IFN receptors have been published (Furie et al., 2017; Morand et al., 2020), and anifrolumab has been approved by the FDA for the treatment of patients with lupus, although a clear subpopulation of patients especially susceptible to this treatment has not been identified yet.

In summary, we are still far away from practicing precision medicine in rheumatology. Strategy studies with characterization of the disease or disease subtypes might help to identify specific predictors of response and non-response and to develop individualized treatment approaches.

Prevention of Rheumatic Diseases

It is likely there would be no argument that preventing a disease is better than treating it, especially in rheumatic diseases where no cure has been discovered once the disease is apparent. The World Health Organization developed recommendations for disease screening and prevention. Overall, these recommendations suggest that diseases targeted for screening and prevention should have an important impact on health, an identifiable asymptomatic (or minimally symptomatic) period, during which individuals at high-risk for future disease can be accurately identified, and that there be available an effective means for preventing the further evolution of disease (Wilson and Jungner, 1968; Finckh and Deane, 2014).

Prevention strategies are typically categorized into primary, secondary, and tertiary interventions (Finckh and Deane, 2014). With primary prevention, researchers try to avoid the development of disease by eliminating specific risk factors or increasing an individual´s resistance to the condition, similar to vaccination against infections (Finckh and Deane, 2014). Secondary prevention strategies attempt to reduce progression from a latent or asymptomatic phase of disease to symptomatic disease, trying to interrupt mechanisms of disease development, as done by early identification of cancers through programs such as mammograms and colonoscopies (Finckh and Deane, 2014). The aim of tertiary prevention is to delay or limit the impact of an established disease, and this is how clinicians currently deal with most rheumatic diseases (Finckh and Deane, 2014).

As the knowledge on risk factors for the development of rheumatic diseases grows, it would be advantageous to introduce primary prevention in rheumatic diseases.

Environmental risk factors are of great interest for a preventive strategy of rheumatic diseases, as they are potentially modifiable.

Smoking and other airway stimuli such as silica dust act as environmental factors for the development of antibodies to the citrullinated protein antigen (ACPA)-positive subset of rheumatoid arthritis (Klareskog et al., 2010). Avoiding these risk factors is a practicable primary prevention strategy for RA (Liu et al., 2019).

It has been shown that most patients with RA develop ACPA antibodies many years before development of the disease (Nielen et al., 2004). In some individuals the presence of ACPAs may be accompanied by increased levels of proinflammatory cytokines in blood, and this stage may be followed by non-specific signs of arthritis and eventually by development of polyarthritis fulfilling diagnostic criteria (Finckh and Deane, 2014). All this information provides a "window of opportunity" for secondary prevention. Although an exciting theory, attempts to prevent the development of RA in clinical trials have been unsuccessful so far (Deane and Holers, 2021; O'Neil and Deane, 2021).

In lupus, smoking has also been found to be a risk factor, although not as extensively studied as in RA.

Sunlight is otherwise the most well-known exposure that enhances disease flare-ups, and most probably lupus development too (Klareskog et al., 2010). Hydroxychloroquine has a proven effect in tertiary prevention in lupus and perhaps some effect even in secondary prevention (Finckh and Deane, 2014).

In neonatal cardiac heart block associated with the presence of high antibody titers against the Ro52 protein in women with SLE and Sjogren's syndrome, it is possible to prevent the damage to the fetal heart by treating the mother with high doses of steroids between weeks 20–24 of gestation, another example of primary prevention.

Several modifiable risk factors have been identified in psoriatic arthritis (Soriano, 2019). Evidence that weight loss is beneficial for primary prevention of psoriasis and PsA development is accumulating, and difficult to dispute (Soriano, 2019; Green et al., 2020). For secondary prevention, there is some evidence that identifying and treating subclinical enthesitis in patients with psoriasis might prevent the development of psoriatic arthritis (Soriano, 2019). Finally, there is some controversy on whether effective treatment with biologics of patients with psoriasis might be able to prevent the development of psoriatic arthritis in these patients (Soriano, 2019; Acosta Felquer et al., 2022; Meer et al., 2022).

In summary, new strategies including early diagnosis and treatment, the treat to target approach, remission as the treatment objective, and patients' participation in therapy decisions, plus the development of new effective treatments have changed the expectations of rheumatologists and patients alike. There are still some challenges such as long-term safety of current treatments, and a more individualized and effective treatment of different subgroups of patients. The future is likely the prevention of the development of rheumatic diseases.

AUTHOR CONTRIBUTIONS

ERS wrote the manuscript, and approved it for submission.

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