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VIEWPOINT

On difficulties to define prognostic factors for clinical practice in rheumatoid arthritis

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ABSTRACT

In rheumatoid arthritis (RA), the identification of prognostic factors (PF) capable of predicting disease outcome, response to treatment or success of dose reduction is an important issue, as these factors are intended to serve as a basis for decision-making. The task is complex from the outset, as the definition of disease prognosis or therapeutic prognosis is not uniquevocal. The heterogeneity of the definitions used partly explains the failure to identify PF that can be applied at an individual level. But other factors also contribute. First, the scope of the disease studied is too broad, including nosologically different entities. Second, potential PF are only measured at a single point of time, whereas changes over a period of time should be taken into account to a greater extent, not forgetting the potential impact of the treatment received during this period. Beyond these limiting factors, one of the main obstacles to the identification of PF is probably the fact that the phase of the disease is not sufficiently taken into account. Predicting the disease outcome when it is well established is a more complex challenge than when it is just beginning, as many factors are likely to interfere. The same applies to therapeutic PF, which should be determined according to disease duration. Difficulties also arise from the approaches used, which are often restricted to a single field of interest whereas they should be much more integrative and call on new large-scale data analysis tools with a view to precision medicine.

In RA, prognosis can be defined at two levels: disease outcome, including joint damage and risk of extra-articular manifestations and/or complications, and treatment outcome, including response to therapy, risk of adverse effects and drug-free remission.

DISEASE OUTCOME

Classical definitions of disease prognosis

Disease outcome has been assessed in different ways, using different definitions reflecting disease activity, structural damage, function, quality of life, pain, occurrence of extra-articular manifestations, etc. In addition, it has been evaluated either at a single point of time, such as the achievement of remission, or by considering changes in parameters over a period of time, as is the case for structural damage. This heterogeneity in the definition of prognosis has led to the identification of a large number of factors likely to influence disease outcome, a large proportion of which (genetic, bone, inflammatory biomarkers, etc) cannot be used in routine clinical practice.

So what is the best definition of prognosis? In pivotal and observational studies, poor prognosis is defined as the absence of remission or radiographic progression.[1] Is the latter really the most appropriate? This parameter has the advantage of incorporating all events occurring during the course of the disease. But it has many limitations. What value can be placed on the radiographic progression of existing lesions or on the progression of lesions in joints with little functional impact? This is certainly of interest in the early stages of the disease, especially if we use the definition of rapid radiographic progression (RRP), characterised by a variation in total Sharp score of ≥5 points over 1 year after initiation of disease-modifying antirheumatic drugs (DMARDs).

Approved and validated poor prognostic factors (PPF)

Using definition of RRP, several poor prognostic factors (PPF) have been identified, namely high articular and systemic disease activity (composite score or score component), initial structural damage and the presence of high titers of autoantibodies (rheumatoid factors, anticyclic citrullinated peptide (CCP)). These PPF have been included in national and international recommendations to aid therapeutic decision-making in the context of RA resistant to at least one initial conventional synthetic DMARD.[2]

However, it is not specified whether only one of these PPF should be taken into account, or whether the concomitant presence of several of them should be considered. A partial answer is provided by matrices

assessing RRP risk and taking into account these PPF. These matrices have the advantage of estimating this risk according to different values of the patient's initial characteristics at the start of treatment (usually methotrexate or leflunomide), and of defining subgroups in this way, which makes their application more reliable at an individual level as a test of RRP probability, without however proposing a binary prognostic score.[3] This is undoubtedly one of the reasons why the recommendations are only partially in line with clinical practice, since rheumatologists seem to take into account, in addition to the usual PPF, comorbidities as well as imaging data, particularly inflammatory lesions detected by ultrasonography, while they seem to be of interest above all as a prognostic factor of relapse in the remission phase of the disease.[4 5] Finally, it remains important not to rely too heavily on classical PPF for decision-making. Indeed if immunological status is taken into account, immunonegative patients have the same disease outcome as immunopositive patients and also require intensive treat-to-target (T2T) therapy. More generally, there does not appear to be any relationship between the presence of PPF and the outcome of the disease or response to treatment, as illustrated in the BeSt and IMPROVED therapeutic trials where the endpoint was damage progression which was prevented by the treatments received. This raises the question of defining other disease outcomes. [6 7]

Relevance of other PPF

As a result, these PPF are part of a flexible perimeter that includes (1) validated PPF highlighted in recommendations and taken into account in clinical practice, (2) PPF with a certain level of evidence such as inflammation highlighted on imaging, not included in the recommendations and matrices, taken into account in clinical practice and (3) PPF with a lower level of evidence, not included in the recommendations, taken into account in current clinical practice, such as certain comorbidities[8] or extra-articular manifestations.[9] It is important to note that the PPF used in the international recommendations may be different, since those defined by the American College of Rheumatology 2008 included extra-articular diseases.[10] How can these differences be explained? If we refer to the criteria validated by recommendations, two of them confer a higher risk. These are the initial presence of erosions and anti-CCP. Are these really PPF when they represent the hallmark of the disease? In fact, the disease studied is generally too broad in scope, including potentially different entities, as in the case of so-called immunopositive RA and immunonegative RA, this latter certainly including a proportion of RA cases that are probably immunopositive but not detected by currently available tests, but also, and above all, a wide variety of different diseases (spondyloarthritis, calcium pyrophosphate deposition rheumatism, etc).

It therefore seems essential to better target the study population by considering only immunopositive forms, which implies a better characterisation of RA according to immunogenetic phenotypes (associated with certain immunological biomarkers such as autoantibodies other than ACPAs belonging to the antimodified protein antibodies family, whose production results from the interaction between certain human leucocyte antigens (HLA) or non-HLA genes and environmental factors) to enable a more reliable identification of PPF.

Points to consider for identification of reliable PPF

As for disease activity parameters, the question arises as to whether a single measurement, at the time of treatment initiation, is sufficient to predict prognosis. Several studies seem to show that it is the cumulative values of the number of swollen joints and C-reactive protein (CRP) that are associated with a poorer disease prognosis.[11 12] Thus, for certain factors with prognostic potential, a kinetic rather than a static approach seems more relevant, but it comes up against the potential impact of the treatment received during this period since some changes in transcriptional profiling from peripheral whole blood can be observed, depending on drug mechanisms of action.[13] Moreover, treatment is rarely taken into account when identifying PPF, even though the degree of exposure to one or more DMARD, in terms of duration and dose received, may have an impact on the disease outcome.[14]

Define PPF according to the stage of RA with remission as the objective

The choice of structural damage to define the prognosis of the disease is open to question, given the lack of relationship with function and quality of life.[15] Should we refer to remission? The choice of this criterion is also open to criticism, given the existence of a large number of composite scores whose threshold values for defining remission do not rule out the persistence of clinical or subclinical inflammatory joint disease, and also the fact that assessment is often carried out at a single stage, whereas sustained remission should be the goal. Beyond these elements, the question arises as to whether the definition of remission should be based on the stage of the disease or not. In the early phase of the disease, the choice of a classic composite score is undoubtedly sufficient, whereas in the advanced phase, it is probably less appropriate. In fact, in recent RA, the adoption of the T2T strategy, with close follow-up and therapeutic adjustment according to disease activity, enables this objective to be achieved. This is not the case in established RA, where follow-up is more spaced out, and the perception of the disease by the practitioner and the patient tends to diverge.[16] It is therefore necessary to differentiate between disease activity and other symptoms (pain, particularly that linked to a process of central hypersensitisation, fatigue, sleep disorders, anxiety/depression, etc) experienced by the patient. This suggests that the 'dual T2T' concept proposed by Ferreira *et al*, based on a dual management of the disease—on the one hand, its inflammatory component (using a 3-variable remission score including number of painful and swollen joints and

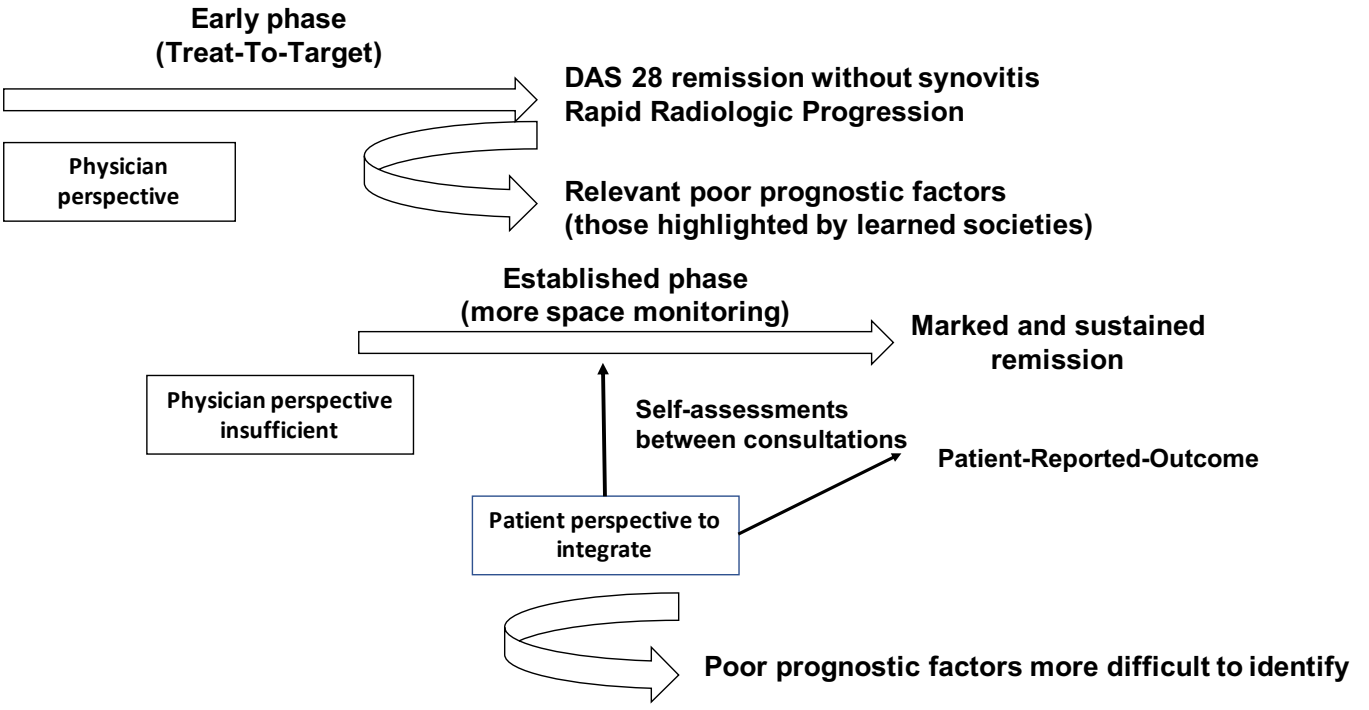

Figure 1 Disease stage plays a major role in identifying reliable poor prognostic factors in rheumatoid arthritis.

CRP) and, on the other hand, the other symptoms, based on multidisciplinary and/or multiprofessional management if necessary—is highly relevant.[17 18] Such a strategy in longstanding RA would avoid therapeutic escalation, particularly with immunosuppressants but also, to a lesser degree, in early RA, where patient–physician discordance can impair disease outcome.[19] Furthermore, as mentioned above, measuring disease activity cannot be limited to assessments during consultations, which are increasingly spaced out in the established phase of the disease. As shown by Welsing *et al*, there are fluctuations in activity that are deleterious for disease outcome.[20] The use of patient-reported indices such as RAPID 3 or FLARE and/or patient self-assessment (meaning the patient can transmit disease informations (scores based on patient-performed joint counts, patient-reported outcomes) via telemedicine, connected tool applications or other remote monitoring methods between consultations) is therefore of particular interest.[21–23] Thus, the definition of prognosis seems much more complex, as it should take into account not only the inflammatory activity of RA, but also patient-reported outcomes and intercurrent relapses. Figure 1 illustrates the importance of taking into account the phase of the disease to define PPF that are adapted to the context.

Several teams have attempted to add a multidimensional character to the definition of remission, in order to be as close as possible to the patient's perspective. This approach, based on clinical, ultrasound and immunological remission, has not been replicated.[24] Such a definition therefore remains to be established in order to identify PPF that are relevant for predicting medium/long-term outcome.

Identification of PPF and/or adoption of the T2T strategy

In view of these limitations, which reduce the chances of identifying PPF that can be applied in clinical practice, the question arises as to whether it still makes sense to attempt to identify them. Indeed, the therapeutic strategy applied in RA, which includes the early introduction of a DMARD particularly in the window of opportunity, and T2T, has demonstrated its ability to prevent structural damage, the occurrence of extra-articular manifestations, and the risk of complications, particularly cardiovascular and bone-related complications. In this respect, the T2T concept has also been extended to other diseases, such as spondyloarthritis, psoriatic arthritis and, more recently, systemic lupus erythematosus.

THERAPEUTIC PROGNOSIS

As for treatment outcome, the same difficulties remain after 25 years of sustained research in this field. However, the identification of predictive factors of therapeutic response is of great interest if we want to offer the right treatment to the right patient at the right time, thus avoiding prolonged periods of disease activity, which are a source of progression of structural damage, and reducing the risk of progression to a disease that is difficult to treat.

Issues for identification of predictive factors of treatment response

Here again, there are many obstacles to the identification of such markers, including the heterogeneity of the populations studied, the definition of therapeutic response and analysis methods, the limited size of the samples studied and, above all, the low proportion of

external validation of the markers identified. In the field of biomarkers, investigations have undoubtedly been too focused on a well-defined field, whatever the approach used, either a priori (genetic polymorphisms, molecular and/or cellular markers of peripheral blood) or not a priori (pharmacogenetics, pharmacogenomics, etc).[25] As a rule, these approaches have led to the identification of several biomarkers of interest, which have not been replicated, or are of insufficient performance and/or difficult to use in routine clinical practice.[26] This issue is probably due to the fact that, in addition to the above-mentioned obstacles, other factors come into play, such as the pathogenic mechanisms of RA, which vary from one patient to another, but also and above all over time, the biological medium studied (as a rule, peripheral blood), which is probably not the most appropriate, the measurement of biomarkers other than genetic ones, which is limited to a single point of time, and the approach used, which is not sufficiently integrative, being restricted to just one omic.

Promising approaches with a focus on the study of the target tissue

Machine learning approaches applied to the identification of predictive factors of methotrexate response/non-response from data available in clinical practice seem encouraging.[27–30] This is why multiparametric approaches of the multiomics type, backed by new analysis tools such as supervised or unsupervised machine learning, artificial intelligence and deep-learning could prove relevant. The question remains, however, whether a paradigm shift is needed, with a focus on the disease's target tissue, namely synovial tissue. The results of the R4RA and STRAP studies demonstrate the value of stratifying patients according to synovial pathotypes to predict response to tocilizumab and rituximab.[31–33] The same approach also seems relevant in psoriatic arthritis.[34] Once again, results vary according to disease duration illustrating the importance of taking the time factor into account in the theranostic approach. In addition, the main limitation lies in the difficulty of accessing synovial biopsies in a practical manner.

Prediction or predictability in the context of de-escalation of therapy

When the patient is in persistent remission, it is advisable to try to taper or even to discontinue the current DMARD. In this context, it would be useful to identify factors that could predict the success of this therapeutic relief. But there are also many obstacles to their identification, whether it is the definition of remission, the heterogeneity of associated treatments or the disease profile. As a result, a large number of PPF have been identified, but their relevance remains questionable due to limited replication, with the exception of a few (disease duration, time to achieve remission on bDMARD (bDMARD, biologic disease-modifying antirheumatic drugs), etc).[35] As in the case of certain PPF associated with disease prognosis, taking into account the sequential course of some of these prognostic candidates during the tapering phase would undoubtedly be of added value from the perspective of predictability rather than prediction, which only takes into account parameters assessed prior to DMARD dose reduction. This refers to the concept of disease activity guiding therapeutic tapering and, in this regard, we showed that, in RA patients in remission under bDMARDs, variation of Simplified Disease Activity Score during the dose reduction phase was more relevant than baseline parameters in predicting the success of drug withdrawal.[36 37]

Proposed research agenda

- To facilitate the identification of new and reliable PPF that can be applied in daily practice to a well-targeted population by conducting studies based on RA populations with well-defined phenotypes (exclusively immunopositive, etc).
- To conduct studies using other outcomes than remission or radiographic damage as poor outcome, taking into account the stage of the disease but also patient self-assessment, for identification of these new PPF.
- To assess the impact of PPF on the disease outcome (remission, structural progression) and on the clinician's treatment decision such as initiation of targeted therapies by categorising RA patients into subgroups defined on the number of PPF.
- To determine whether certain characteristics of the patient (tobacco use, high Body Mass Index and Patient-reported outcome), as well as the modalities of therapeutic management (early initiation of DMARDs, T2T strategy, therapeutic sequences, dose of DMARDs received, etc), can influence the outcome of the disease, independently of the traditional PPF.
- To determine whether predictability (based on variation of one or more parameters over a given period of time) is more pertinent than prediction (based on data measured at a single time) to predict disease outcome, response to treatment or success of de-escalation of therapy.
- To compare new large-scale data analysis tools to those restricted to a single but relevant field of interest (eg, target tissue rather than whole blood) in their ability to predict disease prognosis or therapeutic prognosis.

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