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Editorial

Clinical trials in rheumatology. Does one size fit all?

Identifying the three patient population sets might be the first step

The introduction of biologic agents has allowed great strides to be made in the management of patients with autoimmune rheumatic diseases (ARDs) in the past few decades. We can now effectively deal with various facets of the immune response and the inflammatory cascade that are responsible for the clinical features of ARDs. Examples of improvements for patients are numerous. The prevalence of extra-articular involvement and the severity of disease-related damage and disability have reduced in RA. ANCA-associated small-vessel vasculitides (AAVs), once conveying a prognosis similar to aggressive cancer, are now curable in the vast majority of patients. These results have been made possible by a convergence of interests between practising physicians and medical industries and by a synthetic one-size-fits-all approach, with patients grouped into few inclusive nosologic entities.

The abnormal presence of microbial components in biologic specimens directs diagnosis, classification and therapy of infectious diseases, whereas the identification of the impact on gene function of specific mutations is the key for classification and, when feasible, for the management of monogenic diseases. Biology of the cancer–stroma complex, which is defined by tissue of origin, histological features and molecular markers, plays this role in oncology. ARDs include heterogeneous syndromes for which nosology (i.e. the codification of diseases), diagnosis (i.e. synthetizing patient features into a specific disease previously defined) and the classification of disease subsets are not uniquely defined and are continuously adapted to meet the current medical knowledge. Indeed, the definition of vasculitides has been recently updated [1], and criteria for diagnosis and/or classification (used here with the meaning of definitive diagnosis specific enough for enrolment in clinical studies) are repeatedly refined using the opinion of experts as terms of reference [2].

A synthetic, one-size-fits-all approach is in general ideal for all conditions that depend on single mechanisms to be pathogenic, shared by all or by most patients with that diagnosis. Even if environmental cues and genetically determined predispositions modulate the eventual manifestations of a disease, identifying and targeting single, non-redundant events would provide effective therapeutic strategies. Gene therapy or bone marrow transplantation for monogenic diseases or haemoglobinopathies are examples of this approach. Unfortunately, single pathogenic mechanisms for most ARDs are missing. At present, we lack a clear view of most events that cause the clinical and biological manifestations of ARDs and, specifically, we ignore the precise hierarchy among disease-associated events.

Thus, a reasoning that focuses on the characteristics shared by groups of patients is used for nosography and diagnosis of ARDs. Differences are usually neglected, resulting in substantial heterogeneity in patients with the same diagnostic tag. Translational and clinical research studies use existing nosologic entities as a backbone for patient enrolment, further strengthening the current nosology even when it is not fully satisfactory.

Reducing the complexity of patient phenotypes into a limited number of nosological entities simplifies the life of the physician, providing a reassuring logical framework, facilitating the diagnostic process with clear classification/diagnostic criteria, and highlighting evidence-based management, with important legal implications. Moreover, the reductionist grouping approach ensures that medical industries have a greater number of potential customers. However, even such a successful approach has limitations. Trials studying new agents for ARDs comprise at least three population sets of patients: those responding to conventional treatments, in which limited additional benefit can be expected; those responding substantially better to the new medication; and those not responding either to the conventional or to the new regimen. As treatments become more and more effective and the number of patients not reaching a specific outcome with standard therapy progressively decreases, the average advantage of novel therapies in large and heterogeneous groups of patients cannot but diminish while the number needed to treat increases. Thus, trials need progressively to increase their sample size. We believe that this approach, although useful for clinicians and possibly lucrative for companies, might be inefficient and involve greater expenses for trials and for clinical management. The majority of patients receiving a novel, costly medication on the basis of new evidence and recommendation may not genuinely benefit or need it.

Could alternative strategies be developed? Characterization of the above-mentioned three population sets, focusing on patients' distinctive features rather than on similarities, might be a first step. For example, it is accepted that the expression of serological disease markers, autoantibodies in particular, can be used to identify subsets of patients that are relatively homogeneous in terms of clinical features or prognosis. This is, for example, the case of AAVs or of RA. The presence of ANCA in patients with eosinophilic granulomatosis with polyangiitis is associated with more extensive vasculitic

manifestations, and ANCA antigen specificity is more closely associated with disease features, genetic predisposition and prognosis than clinical diagnosis [3, 4]. RF and ACPAs positivity is associated with severity and with some clinical features of RA, including the presence of extra-articular manifestations and the accelerated erosive involvement (e.g. see Aletaha *et al.* [5]).

Serological disease markers can be used to identify relatively homogeneous subsets of patients, which has an impact on the response to treatments. ANCA specificity represents an independent factor predicting relapses in patients with AAVs, whereas RF might predict the response to rituximab and tocilizumab in patients with RA [6]. ANCAs, ACPAs and RF are not only disease markers but also players in the disease pathogenesis. This might be relevant for their ability to identify patients who respond (or fail to respond) to treatments. In general, we believe that the identification of biomarkers that are associated with the pathogenesis of ARDs could lead to identification within patients taking the same diagnostic tag subsets who are more likely to benefit from novel treatments. Expression or titres of soluble molecules, molecular and functional imaging studies, and morphological or biomolecular tissues evaluations could all, in principle, contribute to split patients into more homogeneous groups.

This could be a priority in the research agenda for the next few years; on the one hand, shedding light on the heterogeneity within existing nosologic entities, possibly resulting in the identification of a plurality of diseases among those that are inscribed in currently coded nosology, and on the other hand, making smaller and cheaper studies possible and informative.

The research funded by the medical industry cannot be asked to work in this direction. Rather, it is the duty of academic research to overcome the one-size-fits-all approach. Sponsored research may choose to follow new findings later. Academic research, which has the aims not only to improve knowledge and medical management of rheumatic patients but also to increase the efficiency of the whole system (by reducing expenses for drug administration and trial implementation), needs economic support. This investment by the National Health Systems will be rewarded with good interest for the community, making the development of treatments at a lower cost possible and enabling more effective patient care.

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