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Towards Precision Rheumatology ?

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Abstract

The possibility of tailoring treatment on specific characteristics of patients – i.e. personalized medicine – has received attention in the field of rheumatic diseases since biological DMARDs targeting a unique pathway have become available. However the idea of personalized rheumatology has advanced slowly, at different paces in different disease groups, and it is only now surfacing in the recommendations for assessment and treatment of rheumatoid arthritis (RA). Many of the difficulties encountered stem from the recognition that many rheumatic diseases are not a single entity but encompass different subsets identified on the basis of genetic traits, cellular and molecular characterization both in blood and in tissues, laboratory markers and clinical manifestations (most notably in SLE). These differences suggest a multiplicity of pathogenetic triggers, whose various combination results in slightly or very diverse presentations. Developments in companion diagnostics and the identification of distinct subsets within complex syndromes are going to allow the definition of predictive biomarkers able to reduce poor treatment outcome, thus ensuring that we are treating "the right patient with the right drug".

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Background

It is becoming increasingly clear that most nosological entities in rheumatology are heterogeneous, both pathogenetically and clinically, so that the era of the new biologic disease-modifying anti-rheumatic drugs (b-DMARDs) which started with great hopes is now confronted with the dilemma of choosing the right drug for the right patient [1]. Diseases such as rheumatoid arthritis (RA) are multifactorial and chronic in nature. As in many areas of medicine, many drug families are available to clinicians to manage these d isorders but few tests exist to maximize outcomes and deliver safe and cost-effective care[1]. As a consequence, drug failure and switching to drugs with different modes of action is common.

This is more obvious for RA, but it is apparent in several other diseases, from systemic lupus erythematosus (SLE)[2] to systemic sclerosis[3], Sjögren's syndrome[4], psoriatic arthritis[5] and ANCA-associated vasculitis[6]. Stratification of patients for treatment implies the definition of well identifiable subsets that exhibit differential outcomes and responses to specific therapeutics[7]. Targeted therapeutics is just one of the many fields where rapid identification of subsets within recognized diseases may improve health quality and survival and at the same time cut the rising costs of treatment. Selection of patients for new clinical trials may reduce drug failures, and also be predictive of the outcome for marketed treatments. Moreover, biomarker (s) discovery can provide focused guidance to molecular pathways to target with available drugs, or with the development of specific active new drugs. Therefore the whole concept of precision medicine is to improve diagnosis and prognosis, target therapy, assess response to treatment, and further our understanding of the pathogenesis of disease[8]. This goal can be attained with the aid of laboratory tests which measure biological indicators or 'biomarkers' of disease activity, autoimmune status, or joint damage[9]. Despite the widespread recognition that specific subsets of rheumatic diseases exist[10-12] a consensus on how many subsets can be easily discriminated and by which criteria has not yet been reached. The rate of progress in the fields of proteomics, genomics, microbiomics, imaging, and bioinformatics poses in itself a problem of defining a paradigm in an ever-changing landscape; another problem is how integration of these technologies into clinical practice could support therapeutic decisions, an area where agreement derives also from evaluation of outcomes of field studies. As stated in a recent EULAR publication[13], "personalised medicine, new discoveries and studies on rare exposures or outcomes require large samples that are increasingly difficult for any single investigator to obtain" therefore a multistep, international consensus process was carried out, to define items to collect in order to facilitate collaborative research, allow for comparisons across studies and harmonise future data from clinical practice[13].

Some Examples: SLE

The definition of classification criteria for SLE, as convened in the published consensus from 1982 and subsequent 1997 update [14-17] clearly illustrate the absolute heterogeneity of the syndrome, where several combinations are allowed to define the patient's diagnosis irrespective of the fact that two patients may not share a single feature. Many aspects have been defined, such as changes with the age of onset[18, 19] (juvenile onset of rheumatic diseases has always been assumed to represent distinct clinical entities[20], and the definition of adolescent rheumatic disorders has just started to surface[21]), the cutaneous aspect, the kidney damage classification, the association of antiphospholipid syndrome, and more recently the neuropsychiatric aspects etc. [16, 22-25]. Among these sets of classification criteria (which are not diagnostic, although frequently misused) the latest version of 2012 has tried to capture the enormous variety of clinical, immunological and laboratory findings in SLE[26, 27]. If these have improved the ability to identify lupus patients, doubts remain on their usefulness to provide significant advances in the management of SLE[28]. New insights into SLE pathogenesis have come from the recognition of an interferon type I signature and the involvement of NETosis of neutrophils in the generation both of this response and the development of autoantibodies against nucleic acids. Both new biomarkers and novel genetic risk loci for SLE have been more recently identified[29], but there is a long way to assess new candidate criteria definitions and organization based on operating characteristics[30]. Moreover, their use for diagnosis, disease monitoring, predictive value and applicability in clinical practice are open questions. As reported[31] SLE diagnosis still represents a challenge, remaining largely based on a clinical judgment. Besides SLE diagnosis, even its classification is still challenging to date, although the classification of SLE seem s to be better achieved with the 2012 SLICC criteria[27]. Still, this does not help for targeted therapies: m any promising early phase studies have ultimately been disappointing in phase III, randomized, controlled studies[32]. Recent efforts have focused on B-cell therapies, in particular, belimumab [33] after rituximab[34], with limited success, due to the difficulty to target pathogenetically relevant B subsets[35]. Other specific therapies are being evaluated, including interferon-alpha blockade, which should work better in a subset of SLE patients with high vs low type I interferon levels[36], taking also into account that clinically quiescent disease has a higher prevalence of anti-IFN-alpha autoantibodies[37]. It is likely that in SLE, given the heterogeneity of the population involved, and the wide range of organs involved[38] precision medicine is needed, with the aid of tissue-specific biomarkers.

Other Connective Tissue Diseases and Vasculitis

The revolution in technologies for gene expression profiling and biomarkers discovery has affected the perception of other complex rheumatology diseases such as systemic sclerosis[39] where distinct subsets had long been recognized on clinical and laboratory basis[40]. This occurred despite the absence of real advances in the treatment of these diseases, but validated biomarkers from a genomic and proteomic analysis, serum antibody and molecules and surrogate measurements of clinical endpoints[41, 42] may be used as predictors for disease outcomes. Meta-analysis of genomic changes in clinical trials[43] may also provide better interpretation and tissue specificity of the effects of treatments.

On the opposite front, psoriatic arthritis – a condition where multiple therapeutic options are available, targeting several molecular pathways – has been investigated for the lack of clinically useful biomarkers predictive of therapeutic response[44]. Two recent systematic reviews of all available treatments have concluded that differences in baseline characteristics may explain some of the differences in response to biologics versus placebo across different trials[45], and recommendations for a sequential biologic treatment based on patients stratification have been proposed[5].

Limited experience comes from studies of predictive cellular biomarkers in Sjögren's syndrome treated with anti-CD20 for B cell depletion, both in biopsies of target organs and in peripheral blood[4, 46], probably for the dissociation of biological and clinical outcomes, despite in large trials some beneficial effects were observed. The same can be said for vasculitides, where the distinction based on the size of arteries involved and presence of anti-neutrophil cytoplasm antibodies (ANCA) is well established and recent insights indicate that distinct patient subsets may actually exist, justifying the development of more personalized management strategies[6, 47].

From Autoantibodies to Complex Immune Monitoring

A clinical disease entity (RA or SLE, for example) is diagnosed by means of established features which distinguish that disease from similar ones; however in the absence of etiopathogenetic knowledge, very few biomarkers are available to improve a clinical diagnosis of symptomatic disease. Some may be useful for early asymptomatic diagnosis in at-risk populations, but what is now needed are biomarkers endowed with prognostic and predictive significance, as well as the assessment of response to therapy or disease progression [48]. In these latter functions, nonspecific inflammatory markers or autoantibodies are not performing reliably. A useful marker should be a characteristic that can be objectively measured as an indicator of either normal or pathologic biological processes, or as an indicator of response to treatment[7]. One or more biomarkers can be adopted, in a panel comprising a combination of disparate types of feature, such as radiographic, histologic, cellular, proteomic, and genetic variables. The simple lesson derived from observational studies indicates that one nosological entity often comprises several distinct disease subtypes that can differ subtly in clinical presentation but markedly in molecular phenotype. Understanding the molecular pathogenesis of disease is essential for the development of mechanistic biomarkers [8, 48].

Both diagnostic, prognostic and predictive biomarkers can be studied together in the growing field of 'companion diagnostics' which could greatly advance disease management[9, 49]. Efforts are increasingly being made to use new insights of molecular pathogenesis to identify mechanistic biomarkers in rheumatic diseases[50, 51]. This approach has revolved around cytokine levels as biomarkers for disease activity and response to therapy (anti-cytokine therapies) particularly in arthritis[52, 53]. However they have been used for autoinflammatory diseases - known to be driven by IL-1, and as mechanistic biomarkers for SLE, with focus on type I interferons, with some patients showing high levels in the blood, as well as a signature of type I interferon-associated gene expression in their circulating immune cells; the latter represents more unbiased evidence since measuring type I interferon directly can be misleading because of many different isoforms. Autoantibodies are also emerging as useful, possibly mechanistic, biomarkers for some autoimmune rheumatic diseases. Autoantibodies that bind to and form immune complexes with DNA, RNA or chromatin autoantigens implicated in SLE augment type I interferon production in plasmacytoid dendritic cells, and specificities of antibodies to citrullinated proteins (ACPA) may differentiate RA subsets (see below).

In addition to inflammatory cytokines, different immune cell types can also distinguish different subtypes of the same clinical disease. Focusing on cell types as stratifying biomarkers is a relatively new area of research, which is gaining attention after initial attempts made with type I interferon signature in SLE and B cell phenotyping for assessing response to B cell depletion therapy with rituximab [1]. B cells have obviously attracted attention also for characterizing subsets in Sjögren's syndrome[4, 54].

New technologies, including mass cytometry, next-generation sequencing and gene expression profiling by RNA sequencing (RNA-seq) and multiplexed functional assays, now allow the analysis of immune cell function with extreme detail, i.e. at the single cell level[55]. The use of these technologies produces very large data sets, which need new computational methods for data analysis and visualization. But the most striking message from these applications is a new way of disaggregating (within the same disease) and reaggregating (across different diseases) features defining discrete subsets. The emerging concept is that rheumatic diseases can be classified according to similarities in pathogenesis or therapeutic responsiveness[55].

Biomarkers and Heterogeneity in RA

Biomarkers in rheumatology can help identify disease risk, improve diagnosis and prognosis, target therapy, assess response to treatment, and further our understanding of the underlying pathogenesis of disease[8]. The management of RA has been dramatically transformed with the advent of b-DMARDs, but since these are targeting different molecular pathways, it is even more irrational to observe that individual patients are treated sometimes sequentially with different drugs, selected using little mechanistic rationale[1]. This leads to increased costs, unnecessary toxicity and frequent failures, i.e. treatment way below the expected effectiveness[56]. Furthermore, the varied response pattern reflects the increasingly recognized concept of RA as a *syndrome,* with many immunological variants and a common clinical phenotype.

The principle of personalized medicine is to deliver targeted therapies according to the individual patient profile and disease endotype. This has prompted the search for reliable response predictors, both clinical and biological. Some predictive biomarkers have been analyzed across several clinical trials[57] and found to be consistent but of limited applicability. In RA, ACPA autoantibodies target a wide variety of citrullinated antigens, and citrullinated fibrinogen bound to autoantibodies induces macrophage tumor necrosis factor (TNF) production[55]. Seropositivity for ACPA identifies a subset of RA patients which has a more destructive course, requiring a different approach from seronegative cases[58, 59]. Precision targeting of therapy has been evaluated both in respect of methotrexate[60] treatment outcome, and of biological therapy with the identification of a myeloid complex signature[61]. Another approach has been made with analysis of inflamed synovia and transcriptome expression[1, 55], more recently focused on molecular profiling of fibroblast-like synoviocytes[62]. Expression of CXCL13 mRNA in the inflamed RA synovium is a strong predictor of the presence of germinal centers in this tissue, suggesting that CXCL13 contributes to the autoimmune synovitis in RA and has been found to predict response to different b-DMARDs[1]. While multiomics databanks allow comparisons of several proposed biomarkers as predictive of response of TNF inhibitors[63], data mining and new powerful technologies uncover novel candidate genes[64] and potential biomarkers related to pathogenic cytokine pathways[65] which need in-depth assessment of their predictive value. We should mention that also epigenetic and miRNA biomarkers have been proposed, as well as new insights derived from the expanding field of metabolomics [1]. We recently examined the differential course of RA in the context of visceral obesity (associated with slower structural damage) and the obesity paradox of rheumatoid cachexia, indicative of accelerated mortality[66], as well as the different presentation of RA with aging[67]. These two parameters greatly affect antibody responses and immune cells profiling[55, 68]. The metabolic changes occurring in the development and chronicization of RA have been recently reviewed [69] and they widely differ between early and chronic RA. In the early stages a high metabolic demand (because of hyperproliferation, angiogenesis, and unbalanced bone turnover) is met by a reduction of the glycolytic pathway in favor of the pentose phosphate shunt in T cells[70], reduced ROS generation and decreased AMPK function. In these early stages, a pro-oxidative intervention and AMPK activation may be novel pharmacotherapeutic targets. In the late (erosive) stage of RA, the inflamed joint is a hypermetabolic lesion [69], T cells undergo a metabolic switch to aerobic glycolysis due to hypoxic conditions, with differentiation towards inflammatory Th1/Th17 phenotypes and acidification of the synovia due to lactate production. This stage is preferentially blocked by b-DMARDs, despite the persisting uncertainties on the drug of choice in individual patients and the dissociation between laboratory and clinical outcomes in the absence of precise biomarkers[71-73].

Conclusion

In rheumatology the heterogeneity of clinical presentations indicates the different pathogenetic pathways driving autoimmunity and inflammation at the single organ level. The wealth of new therapeutic options make precision medicine a compelling need to maximize optimal outcomes. We need therefore validated biomarkers, which can be clinical, histological, or imaging parameters as well as specific molecules or molecular patterns (genomic, proteomic, and lipidomic biomarkers) to reflect changes that occur early in the disease process or in the response to therapy. Clinical decisions have to be corroborated by such indicators of therapeutic targets in a more personalized process. The emerging multi-omics approaches (genomics, transcriptomics, proteomics, metabolomics) pose further challenges for interpretation, so that distinctive subsets (or disease endotypes) should be identified to facilitate clinical utilization. The ultimate goal of precision in rheumatology rests in the best use of treatment options, ensuring that we treat "the right patient with the right drug at the right time"[1].

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