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EDITORIAL

Recent advances steer the future of systemic sclerosis toward precision medicine

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The term "precision medicine" has become increasingly popular by proposing a medical model which allows to choose a personalized treatment. Hippocrates, almost 2500 years ago, was himself a proponent of personalized medicine, in fact he advised "give different ones (liquid medicines) to different patients, for the sweet one do not benefit everyone, nor do the astringent ones, nor are all the patients able to drink the same things" [1]. The personalized approach has always been of fundamental importance in the relationship between the physician and the patient and still today continues to represent a significant central part of precision medicine. Previously, treatment choice was largely based only on signs and symptoms presented by patients. However, precision medicine includes an approach to patient with a wide array of individual data including clinical features, lifestyle, genetic, and biomarker information as well as disease symptoms and signs [2]. Hippocrates already suggested to evaluate factors like physical appearance, a person's age, and the time of the year when prescribing medicines [3] to better target drug prescription to individual patients. Therefore, this medical approach may help to predict which is the best treatment in a specific group/s of patients. It is clear that the development of precision medicine has fundamentally changed the treatment approach to several diseases, in particular in neoplastic diseases, using genetic and molecular diagnostics with DNA evaluation. However, its role in every day healthcare is relatively limited to date.

Recently, many significant efforts have been made to better understand the pathogenetic [4] and genetic mechanisms in a broad range of rheumatic diseases. This knowledge could allow to stratify patients and therefore potentially expand a precision medicine approach in the rheumatic diseases field.

Systemic sclerosis (SSc) is a connective tissue disease characterized by autoimmune features, vasculopathy, and fibrosis [4, 5]. Skin fibrosis is a well-known distinctive trait of the disease and the severity of skin involvement has been reported to be predictive of disease mortality [6]. Usually, the disease is classified according to skin involvement extension in a limited and a diffuse subset, but today it is clearly evident that this subsetting does not express the practical reality of the disease [7, 8]. In fact, the disease is characterized by a wide variability in both the clinical phenotype and in progression. In daily practice, clinical parameters are used to attempt to identify homogeneous groups of patients, as the isolated diffusing capacity for carbon monoxide (DLco) reduction characterizing a particular subset of SSc ACA positive patients [9]. An association of muscle involvement and autoantibody profile was recently described suggesting that X-ray findings may identify a precise subgroup of SSc patients [10]. It is also suggested that racial differences can be associated with distinct subsets [11]. However, patients within the same subset may show substantial different disease evolution including organ involvement as well as a heterogeneous response to treatment [12, 13]. The current ACR/EULAR classification for SSc which was proposed in 2013 has significantly higher sensitivity and specificity compared with existing classification criteria [14]. Significant efforts have now been devoted in establishing the very early diagnosis of SSc [15]. To date, clinical trials to recruit homogeneous populations of SSc patients have selected (in general) patients with either early active diffuse SSc or those patients with single internal organ involvement, for example, pulmonary arterial hypertension (PAH) or interstitial lung disease (ILD) [16]. Furthermore,

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recent work which included 11,318 patients from the EUSTAR database using cluster analysis found that restricting subsets to only skin involvement did not capture the heterogeneity of SSc and that organ damage/autoantibody status identified homogenous groups of patients with different prognosis [17].

Against this background, the recent advancements in this field have tried to overcome this clinical picture by providing a more homogenous approach through the genomic emprinting of the patients examining specific drug therapies [18]. Transcriptomics allow for significantly greater characterization of the disease process including the identification of different SSc subsets through the use of intrinsic gene expression analysis [19]. Patients from the same intrinsic molecular subset share common biological process and similar specific signaling pathways.

To date, a total of four subsets have been recognized and validated by multiple studies [20–22]: the fibroproliferative, the inflammatory, the limited, and the normal-like subset. The fibroproliferative subset is characterized by a significant proliferative signature (mitotic cell cycle, chromosome segregation, cell division, and microtubule cytoskeleton) and the platelet-derived growth factor (PDGF) pathway has been suggested to have a relationship with this subset [17]. In the inflammatory intrinsic subset, the gene expression signature is addressing the immune system process, the inflammatory and defense response, and the vascular response. In this subset, a correlation with interleukin 4 (IL-4) and tumor necrosis factor alpha (TNF-α) has been suggested. Interestingly, transforming growth factor beta (TGF-β) appears associated to the fibroproliferative and inflammatory subsets. The limited subset includes patients with "usual" lcSSc, while those with the normal-like subset presents like a clinically active SSc with a molecular signature characterized by a lipid metabolic process, lipid biosynthetic process, and fatty acid metabolism [19, 22, 23]. Of note, upper and lower esophageal biopsies in SSc showed molecular subsets which were equivalent to the inflammatory and fibroproliferative subsets obtained from the examination of the skin [24] which could suggest the presence of similar molecular mechanisms responsible for SSc in different organs and tissues. In addition, previous studies have demonstrated that the same intrinsic molecular subset may include both lcSSc and dcSSc, except for the limited that includes only lcSSc subjects. These data suggest that the four SSc intrinsic subsets span the two current clinically identified subsets of lcSSc and dcSSc disease and that the molecular signaling pathways of each subset may elucidate the clinical phenotypic heterogeneity in SSc population. Recent studies demonstrated a relationship between intrinsic subsets and a clinical response to specific treatments. This evidence may thus introduce the concept of "precision medicine" in SSc. The possibility to characterize every single SSc patient in terms of peculiar molecular pathways may help to identify those patients that could benefit from drugs targeting inflammation (inflammatory subset) and/or fibrosis (fibroproliferative subset) [16, 21]. The inflammatory subset has shown a significant response to immune modulating therapies [13]. In a recent study, all enrolled patients treated with mycophenolate mofetil (MMF), who reached a modified Rodnan skin score (MRSS) improvement > 25% (defined improvers) tended to have an inflammatory pattern at baseline. In addition, their analysis demonstrated a decreased expression of genes related to inflammation, innate immune inflammation, innate immune response, leukocyte differentiation, apoptotic process, and angiogenesis in improvers. Patients with high inflammatory normalized enrichment scores (NES) at baseline seemed to lose the inflammatory signature after MMF therapy. Patients with an increase of inflammatory NES also demonstrated an increase in MRSS after MMF discontinuation. High level of the myeloid cell chemo-attractant CCL2 has been found in the skin of SSc patients with the inflammatory subset and both CCL2 mRNA and CCL2 serum levels decreased during treatment with MMF. Finally, the same study confirmed the role of macrophages [25] and myeloid dendritic cells (mDC) in SSc pathogenesis, as their level seems to decrease during MMF treatment and correlate with inflammatory NES [13]. The use of belimumab and MMF for the treatment of SSc also showed similar results [26], although, authors did not show significant differences in mRSS improvement between patients treated with belimumab compared with placebo. The analysis of differentially expressed genes showed a decrease of genes involved in defense response, inflammatory response, and complement activation only in the belimumab arm. In addition, the baseline difference between belimumab improvers and non-improvers showed the expression of pathways included in ECM-receptor interaction and TGF-βR (TGF-β receptor) signaling. Therefore, authors suggested that a decrease in inflammatory pathways after belimumab therapy and a correlation between the transition from the inflammatory and fibroproliferative subsets to the normal-like one and the reduction in mRSS [26]. In SSc patients, treatment with abatacept was associated with a significant mRSS improvement in particular in those with a baseline inflammatory intrinsic subset (four patients out of five improvers) [27]. The improvers also showed a difference in the expression of nearly 400 genes from baseline to post-treatment. Out of these genes, those with an increased expression after the therapy were related to DNA repair, microtubule cytoskeleton, and mRNA processing. On the contrary, gene associated with immune activation and CD128 signaling were high at baseline and significantly decreased in the post-treatment evaluation in improvers, consistent with the mechanism of action of abatacept [27]. In patients with dcSSc, nilotinib, a tyrosine kinase inhibitor (TKI), after 12 months of therapy was associated with an improvement in mRSS (defined as change > 20%) in patients with a high level of TGF-βR and PDGFR-β (PDGF-β receptor). Between the four improvers, three were classified as non-fibroproliferative subset at baseline,

two with the inflammatory subset and one the normal-like subset. After the treatment, out of four improvers, three were classified as normal-like. Of note, the two non-improvers were classified at baseline as fibroproliferative subset. These results are in agreement with previously reported data suggesting that TGFBR signaling seems to span the inflammatory and fibroproliferative subsets [28]. In another study, the effects of dasatinib in SSc patients with interstitial lung disease (ILD) [27] was evaluated. Skin biopsies were assigned to one of the four specific subsets; three subsets were observed (fibroproliferative, inflammatory, and normal-like) as no lcSSc patients were enrolled in the study. Four patients classified as clinical improvers were all non-inflammatory presenting or the normal-like pattern (two subjects) or the fibroproliferative one (one patient) which suggests that dasatinib seems to more likely benefit SSc-ILD patients with the non-inflammatory subset [29]. A meta-analysis suggested that after treatment, improvers are typically characterized by a decrease in immune and fibrotic signaling. However, therapies classified as "immunomodulatory," for example MMF and abatacept, might act on different pathways. On the contrary, fresolimumab (an anti-human TGF-β antibody) might be useful in patients with elevated levels of TGF-β at baseline but not in those with increased baseline immune-related gene that could benefit from MMF therapy. These data could suggest that precision medicine could often take advantages from a combination therapy approach [30].

On the other hand, it is also important to identify patients at risk for disease progression in skin or internal organs involvement. In practice, the severity of skin involvement may represent an important clinical feature indicating the evolution of the disease. In this perspective, the relationship between change in gene expression and mRSS progression has been investigated [31]. With the aim to predict the trajectory of skin disease in dcSSc, the skin gene expression has been investigated from patients enrolled in the FASSCINATE study (a phase 2 randomized controlled trial of tocilizumab). The results showed that skin genes associated with the progression of skin disease correlated to TGF-β (SERPINE1, CTGF, OSMR) or macrophages (CD14, IL-13RA1). In addition, patients with a "progressive trajectory" of skin score presented with a higher mRSS at baseline and higher expression of the abovementioned genes at baseline when compared with both patients with regressive and stable trajectory [31]. This suggests that patients at risk for a severe skin progression may be identified based on genetic markers. In the same context, a recent study investigated the possibility to distinguish patients with PAH from those with ILD at molecular level [32]. Authors demonstrated that patients with PAH showed a different genomic signature from those with ILD reporting a positive correlation of S100P, CCL2, and TIMP genes to PAH when also patients with ILD were included in the analysis. When patients with ILD were excluded, the most predictive gene of PAH was THBS1, which is an important soluble peptide for the activation of TGF-β. Therefore, a change in serum or skin levels of specific molecules or genes might predict the response to drug therapies because baseline expression levels of pathways may be modulated by treatments [16]. A recent trial of idiopatic pulmonary fibrosis (IPF) showed a reduction in circulating proteins, μRNA and citokines related to senescence-associated secretory phenotype (SASP) after treatment with desatinib, and quercetin (a kinase inhibitor and a a natural flavonoid respectively) [33]. In SSc-ILD improvers (decrease > 5 points or > 20% in mRSS from baseline) from baseline to the post-treatment period, the skin SASP gene signature levels significantly decreased after treatment with dasatinib [29, 34].

Taken together, these results could represent an important turning point in the management of SSc, highlighting the possibility to choose for each patient the best therapy based on molecular subsetting. Using baseline expression analysis from skin biopsies may represent a valuable tool to select the most appropriate therapy to specific SSc-manifestation/s (e.g., ILD) [29]. Recently, the possibility to classify molecular signatures in intrinsic subsets [19] may offer the possibility to stratify patients allowing the early treatment with the most effective therapy based on their specific gene expression. In SSc, the possibility to employ a precision medicine methodology could become strategically important to provide the best tailored therapy for the disease, including enriching the clinical trial design.

In conclusion, the possibility to achieve a precision medicine approach to SSc patient's organ involvement and subsetting is slowly becoming a reality. Molecular signatures could identify specific disease subsets, driving the choice of anti-inflammatory and/or antifibrotic drugs. The molecular phenotyping of SSc patients might thus allow a precision medicine approach to apply to every patient. Future studies are warranted to confirm these exciting data and provide a new vision about the subsetting of SSc patients in clinical practice.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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