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From mechanisms of action to therapeutic application: A review on current therapeutic approaches and future directions in systemic sclerosis

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A B S T R A C T

Systemic sclerosis (SSc) is one of the most complex connective tissue diseases. Although the pathogenesis of SSc still remains elusive, it is generally accepted that initial vascular injury due to autoimmunity might result in the constitutive activation of fibroblasts and fibrosis. All of these three processes interact and affect one another resulting in a polymorphous spectrum of clinical and pathologic manifestations of SSc. The disease pleomorphism poses numerous difficulties in defining the ideal outcomes to be used in clinical trials. Despite significant progress over the past decades, the clinical management of patients with SSc remains a challenge. Novel therapies are currently being tested in the treatment of SSc and have the potential for modifying the disease process and improving the clinical outcomes. However, the evaluation of the studies is still difficult, due to either the small size of included patients or the different types and phases of the scleroderma disease under scrutiny.

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Introduction

Systemic sclerosis (SSc) is a multifaceted systemic autoimmune disease. Its pathogenesis classically recognizes three different main mechanisms, that is, microvascular damage, autoimmunity-mediated inflammation and fibroblast activation, which may variably interact with each other in the various phases of the disease [1,2]. The complex interrelationship among the three pathogenetic aspects of SSc results in a wide spectrum of clinical presentations, inducing various degrees of skin involvement, microvasculopathy and more or less severe involvement of different internal organs. The advances in the knowledge of the pathogenetic mechanisms and clinical aspects of the disease have allowed defining a more precise classification of different patient subsets.

On the basis of the extent of skin changes, patients are usually classified as limited cutaneous (lcSSc), and diffuse cutaneous (dcSSc) subsets [3]. This classification is also justified by the fact that the two clinical subsets express distinct autoantibody profiles, and different patterns of skin and organ involvement, disease progression and outcome [4]. Unfortunately, many SSc patients cannot fall within such a rigid classification, and the identification of new additional antibodies and biomarkers enriches the heterogeneity of clinical scleroderma pictures. Besides the variability of clinical presentation and evolution and autoantibody associations, the present knowledge of the disease pathogenetic mechanisms makes it evident that SSc cannot yet be considered a chronic disease with an indolent course. Like other rheumatic diseases, it has flare and remission phases. Keeping in mind these considerations, it appears evident that a comprehensive therapeutic strategy has to consider the particular clinical features of the single patient, as well as the underlying immunomediated inflammatory activity, microvascular abnormalities, and fibrotic changes that are operative in the skin and internal organs. Observational studies have demonstrated that in diffuse scleroderma, most of the pathological processes in the internal organs or systems (gastrointestinal, lung, heart and kidney) occur within the first 3 years since the disease onset [5]. Consequently, the key issue that has to drive the therapeutic approach to SSc is that the prompt detection and treatment of any new pathological process may offer the opportunity to induce remission, by stopping or preventing disease progression, and thus minimize skin and organ damage. Once the fibrotic process has begun, it can independently progress through a self-perpetuating biological pathway. Thus, immunosuppression or anti-inflammatory drug intervention may be effective in the early stages of the disease, but ineffective once the disease has moved into the fibrotic phase. Moreover, in late-stage disease, an evolved fibrosis might remain quite stable and, therefore, not require any intervention [5]. Hence, similar to other rheumatic diseases, an early diagnosis of SSc becomes an important tool to achieve a satisfying result in its management. Recently, different studies stated that Raynaud's phenomenon (RP), in combination with puffy fingers, characteristic nailfold capillaroscopic changes and SSc-specific autoantibodies, must be taken into account for identifying patients with early SSc who are at risk of developing more severe clinical features [6,7].

Advances in the understanding of pathogenesis of the disorder, although not completely elucidated, have allowed identification of the cell types, mediators and pathways as potential targets for therapy. Hence, at the moment, the idea of a targeted therapy is not just a hypothesis but a fact, even in patients with SSc.

Treatment approach

According to the presently known pathogenetic mechanisms of SSc, the treatment approach should consider the three main pathological actors: vasculopathy, autoimmune-mediated inflammation and fibrosis. No single strategy is available for treating all patients with SSc, but a combination of different therapeutic modalities should be tailored in any single patient in relation to disease subtype, time of onset, progression and involved organ or system. The clinician behaviour should be absolutely addressed to correctly approach the dominant clinical aspects with the aim of preventing the disease progression and its possible severe complications.