Systemic Sclerosis: know more, hope more

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The 4th World Systemic Sclerosis Congress 2016 took place in Lisbon, and the more than 1000 registered health professionals and patients, gathered to learn more about the disease and its current management.

Systemic Sclerosis (SSc) is characterized by vascular inflammation, vascular hyper-reactivity and excess tissue collagen deposition. These pathologic changes lead to macro and microvascular injury and to fibrosis of the skin and internal organs resulting in organ damage. Unfortunately, the exact mechanism and triggers for endothelial dysfunction and perpetuation of pathologic changes are only partially understood and still needing further research.

Since the last few decades and nowadays, the manifestations that most contribute to the increased SSc mortality are lung disease and pulmonary hypertension, accounting for nearly 30% of scleroderma-related deaths[1].

Besides the higher mortality rate, SSc also has a high impact on patients' quality of life becoming a real and heavy burden. Gastrointestinal involvement, Raynaud's phenomenon and particularly, digital ulcers, increase disability and reduce quality of life. Furthermore, dyspnoea arising from interstitial lung disease, pulmonary fibrosis and pulmonary hypertension (PH) also interfere and disable patients to accomplish their routine daily activities.

Therefore, an early diagnosis is mandatory. The new SSc classification criteria (ACR/EULAR 2013)[2] reflects the need to create an earlier treatment window of opportunity, based on a better understanding of the pathophysiology of the disease, recognizing the importance of capillaroscopy in early diagnosis, and the role of the specific SSc autoantibody profile in clinical manifestations and disease prognosis.

Specific SSc autoantibodies are very rare in other diseases, are generally present on disease onset, and do not change over the course of the disease. Autoantibody profile in SSc has been extensively studied but, until recently, was not widely performed/available in routine clinical practice. As its determination is becoming more routinely done, SSc autoantibodies may "work" as predictors of a specific organ involvement, of prognosis and survival, in the several subtypes of the disease, historically just divided in limited and diffuse, based on the extend of skin involvement.

Thus, integrating the knowledge of these various aspects of the disease, rheumatologists can, in a more careful and targeted way, monitor and recognize potential internal involvement organ, as well as, potential complications and introduce treatment earlier. For this to be accomplished, it is important to perform regular patients follow-up and screening for pulmonary hypertension. In what concerns this complication, regular screening clearly improved patient' survival[3].

At present time, there is still no drug that treats broadly all SSc manifestations, targeting and truly acting on the mechanism of fibrosis. Targeting potential fibrosis and vascular mediators is, or has been underway, but not always successful. The paper from Cutolo et al.[4] in this edition, apart from the physiopathologic review, summarizes potential therapeutic targets in SSc.

At this time point, and despite attempts targeting inflammatory, vascular and pro-fibrotic molecules, just few of them are available for clinical practice. Patients are treated based on their clinical manifestations and related severity and, besides pulmonary arterial hypertension and digital ulcers, usually through immunosuppressive agents and symptomatic treatment.

Pulmonary hypertension, if diagnosed as group I of PH classification[5] (Pulmonary arterial hypertension), has an effective therapy, but most SSc patients show other concurrent PH causes as interstitial lung disease, thrombo-embolic disease or left heart dysfunction, making it more challenging to treat.

As so, methotrexate remains the first therapeutic choice. For interstitial lung disease (ILD) cyclophosphamide is used in clinical practice but has only shown modest beneficial effect on lung function and dyspnea[6]. More recently, encouraging results have been documented with mycophenolate and rituximab, and these

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agents may be considered as options in treating interstitial lung disease[7]. The EULAR guidelines for Sistemic Sclerosis are being updated and will be published this year.

But hope arises as clinical trials in SSc are increasing.

Pirfenidone is an oral pyridine compound, and nintedanib is a tyrosine kinase inhibitor including PDGFRα and β (platelet-derived growth factor receptor), FGFR 1-3 (fibroblast growth factor receptor) and VEGFR 1-3 (vascular endothelial growth factor receptor). Both pirfenidone and nintedanib are effective and approved for the treatment of idiopathic pulmonary fibrosis. Nintedanib has already an ongoing trial in interstitial lung disease, in systemic sclerosis patients.

Tocilizumab, a humanized interleukin-6 (IL-6) receptor antagonist initially approved for rheumatoid arthritis demonstrated encouraging results in a phase II/III randomized controled trial in SSc patients, by ameliorating modified Rodnan skin score[8]. These results granted tocilizumab a breakthrough therapy designation for SSc by FDA (U.S. Food and Drug Administration), in 2015. Another phase III trial in SSc patients is also ongoing/recruiting. Other molecules are being investigated with promising preliminary results. The pro-fibrotic transforming growth factor beta (TGF) pathway can be inhibited by fresolimumab and riociguat. Fresolimumab, a monoclonal antibody to TGF beta, improved modified Rodnan skin score in SSc patients (Rice LM et al. Fresolimumab treatment decreases biomarkers and improves clinical symptoms in systemic sclerosis patients. J Clin Invest. 2015;125 (7):2795–2807). Riociguat, a guanilciclase stimulator blocks TGF beta signalling (Dees C et al. Stimulators of soluble guanylate cyclase (sGC) inhibit experimental skin fibrosis of different aetiologies. Ann Rheum Dis. 2015;74(8):1621-5), and has a phase II study underway. Terguride, a serotonin antagonist (5HTR2B), is also expected to have clinical trials in patients with systemic sclerosis, regarding cutaneous and vascular endpoints.

Learning more about SSc manifestations, regular screenings, general care measures and patient education/empowerment is halfway in preventing complications and improving care.

Regarding therapy, SSc is finally getting a "breath of fresh air" and hope in more robust and long-term benefits rises.

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