It's time to treat systemic sclerosis

Systemic sclerosis (SSc) is still one of the most difficult therapeutic challenges in the field of rheumatic autoimmune diseases. However, many developments took place in the last decade, linked to an earlier diagnosis and treatment and better characterization of the clinical and epidemiological profile of the disease. If an early diagnosis of the cutaneous and visceral involvement is established, more efficient organ-specific strategies can be proposed. Within this philosophy, 2009 began with the first publication of recommendations for the SSc treatment by expert members of the EULAR Scleroderma Trials and Research Group (EUSTAR).[1] Another sign of this growing interest is that the current edition of the *Brazilian Journal of Rheumatology* (*BJR*) has two national studies about therapeutics on SSc.[2,3]

Two situations exert striking influence in the treatment of systemic sclerosis: fibrosis and an altered vascular endothelium. Several drugs have been used for its anti-fibrotic activity, especially in diffuse thickening of the skin and interstitial lung disease. The use of cyclophosphamide[4] and immunosuppressants[5] in SSc has been recently described and analyzed. However, the only randomized, double-blind, placebo-controlled studies with cyclophosphamide were only published in 2006,[6,7] with favorable results but without significant statistic expression. The *Scleroderma Lung Study* (SLS), a multicenter study conducted in the United States under the sponsorship of the National Institute of Health (NIH), has evaluated 158 patients using oral cyclophosphamide (or placebo) for a period of one year, and the patients have been followed for a total of two years; there was statistically significant improvement in primary and secondary endpoints.[6] In subsequent years, the SLS Research Group has published several other articles, deeply analyzing different aspects of the study, such as lung function and skin score,[8] the SSc clinical forms,[9] the quality of life,[10] the bronchoalveolar lavage,[11] and assessment parameters of thorax high-resolution computed tomography (HRCT).[12] The other study was the FAST, which evaluated 45 patients with SSc and active alveolitis in England and treated with intravenous cyclophosphamide (or placebo) for 12 months, then using azathioprine for other 12 months. The primary and secondary endpoints were not statistically significant and the statistical trend in forced vital capacity (FVC) improvement was only observed in patients who used cylophosphamide.[7] The results of these two controlled studies have enabled that the cyclophosphamide could be considered and indicated as treatment of SSc interstitial lung disease according to EUSTAR[1] recommendations, which still require further work to consider cyclophosphamide as treatment for aggressive cutaneous features, which are predominant in early diffuse SSc.

In the current edition of *BJR*, Macedo *et al*.[2] have examined the clinical course of nine patients with diffuse SSc and total skin score (TSS) > 30 without severe visceral involvement who made use of intravenous cyclophosphamide for 18 months and were followed at the Universidade de São Paulo (USP). Significant TSS reduction in the 12 months was observed (Mean TSS ± standard deviation (SD): 37.77 ± 4.08 vs. 29.22 ± 8.13, P = 0009), held after 18 months of treatment (Mean TSS ± SD: 26.42 ± 10.08, P = 0.01), without serious side effects. Ten years ago, we also published on *BJR* the experience at the Universidade Estadual de Campinas (UNICAMP) with intravenous cyclophosphamide in the treatment of 45 patients with SSc. Thirteen of them had rapidly progressive diffuse SSc and also presented statistical improvement at the TSS.[13] Further studies with more patients and a longer follow-up are needed to confirm the capacity of improvement of skin thickening with the use of cyclophosphamide in SSc.

Among the vasoactive drugs, there are some with excellent safety profile and efficacy in the treatment of scleroderma renal crisis[14] and pulmonary hypertension.[15] As the patients with SSc present an improvement in their mean survival, events such as the occurrence of digital ischemic ulcers become more frequent.[16,17] The traditional calcium-channel blockers (such as nifedipine and diltiazen) are more effective in preventing new attacks in patients with primary Raynaud's phenomenon.[18] The most complicated ischemic ulcers can be treated with the use of iloprost[19,20], treprostinil[21], bosentan[22,23], and sildenafil.[24,25]

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However, beyond the treatment of crisis, these extremely painful and disabling ulcers should also have a prevention treatment. The EUSTAR group's recommendations for the SSc treatment consider that nifedipine, the prostanoids (especially the intravenous iloprost) and bosentan may be used to prevent the recurrence of ischemic ulcers in SSc.[1]

Two prospective multicenter, randomized, double-blind, placebo-controlled studies (Rapids-1 and Rapids-2), examining patients in 17 centers in Europe and North America, showed that bosentan can prevent the occurrence of new digital ulcers, but not accelerate the healing of ulcers present at the time of randomization, in SSc patients with recurrent ulcers.[26,27] Based on the results of these studies, Mariz *et al*.[3] (at this issue *BJR*), used the oral bosentan in the treatment of active refractory ischemic ulcers in three patients at the Universidade Federal de São Paulo (UNIFESP), contributing to the healing and prevention of the occurrence of new ulcers in a short follow-up of 12 weeks. The different healing responses seem to reside in the heterogeneity of the definition of active ischemic ulcers.[28]

Concluding, for rheumatologists interested in early diagnosis and treatment of SSc, the detailed analysis of different epidemiological and clinical parameters, that govern the different therapeutic responses in the disease, is essential in choosing the best medication for each phase of the development of SSc, thus optimizing patients' expectations, treatment costs and side effects.

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