

Response to: 'Adipose stromal vascular fraction and regenerative therapy in SSc: response to the article by Magalon *et al*' by De Benedetto *et al*

We would like to thank Di Benedetto *et al*¹ for their constructive comments on our recent publication in *Annals of Rheumatic Disease* entitled 'Molecular profile and proangiogenic activity of the adipose-derived stromal vascular fraction used as an autologous innovative medicinal product in patients with systemic sclerosis'.²

Di Benedetto *et al* mentioned that the profibrotic signature of mesenchymal stem cells (MSCs) derived from patients with the diffuse cutaneous form of systemic sclerosis (dc-SSc) has been established from previous works. In line with this, they discussed the potential risk of increasing the fibrotic burden by using autologous adipose-derived stromal vascular fraction (ADSVF) in which MSCs are highly represented.

Although this is a fair question in the context of developing MSCs-based therapy for SSc, we would like to emphasise the fact that the biological findings referred to by Di Benedetto *et al*, may not be fully extrapolated to the ADSVF used in our study. Indeed, the mentioned studies rather relate to MSCs derived in culture from the bone marrow using research-grade reagents that are very different from the mesenchymal cell compartment that we aimed to describe in the non-cultured clinical-grade ADSVF. Indeed, the use of MSCs necessitate an *in vitro* amplification procedure which can have a major impact on the differentiation and characteristics of MSCs,^{3,4} thereby limiting the comparison between native MSCs present within ADSVF. ADSVF is also a complex product whose biological properties result from multiple interactions between various cell subpopulations, and the role of each cell subset remains to be identified. In addition, it is well established that cultured MSCs derived from bone marrow and adipose tissue are quite different populations⁵ and to our knowledge, such a profibrotic profile of MSCs derived from the adipose tissue of patients with SSc was not reported, as recently confirmed by the review from Rozier *et al*.⁶ In 2017, report from the team of the Department of Biotechnological and Applied Clinical Sciences (l'Aquila University, Italy) indicated that MSCs isolated from adipose tissue of dc-SSc may represent a possible therapeutic option as they show similar biological properties compared with MSCs from healthy donors.⁷

From a clinical point of view, we are surprised that Benedetto *et al* omitted to mention that autologous ADSVF, injected in the fingers of 12 patients with SSc (including five dc-SSc) displaying hand disability, was shown to have a good safety profile and a potential efficacy.⁸ In particular, results of Rodnan score applied to the hands, with a follow-up until 2 years, did not indicate any worsening of the fibrosis aspect.⁹

We would also like to emphasise that the potential strength of our study was that it was performed on clinical-grade ADSVF, meaning that the analysed ADSVF correspond to the products potentially injected in the SCLERADEC II randomised placebo-controlled trial (NCT02558543). From our point of view, evaluation of this therapeutic ADSVF makes our findings of particular clinical relevance but limits the amount of ADSVF available for biological investigations. This is the reason why functional angiogenic assays could not be performed on a larger number of samples prepared from various forms of the disease. We fully agree that additional studies are needed to consider whether the limited or diffuse cutaneous form of SSc have a similar impact on ADSVF properties. As suggested by Benedetto *et al*, refinements in the characterisation of SSc-ADSVF profile is still required. Beyond transcriptomic and phenotypic signature, further work should implement accurate

in vitro and *in vivo* functional assays to address the contribution of each of the cellular subsets and their interactive benefit in the modulation of fibrosis, angiogenesis and inflammation. These targeted approaches, together with outputs from the ongoing clinical trials, are needed to further define the optimal strategies for cell-based therapies of SSc.

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