Editorial Commentary

Is the adipose-derived mesenchymal stem cell therapy effective for treatment of knee osteoarthritis?

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We read with great interest the article "*Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial*" by Freitag *et al.*, published in *Regenerative Medicine* last February 2019.

We congratulate the authors for their work, which contains valuable clinical information to understand the effectiveness of the increasingly common treatment of knee osteoarthritis (OA) with adipose tissue-derived stem cells (ASCs). Indeed, literature reports fundamentally two types of treatment based on ASCs: stromal vascular fraction (SVF) (1,2) or *in vitro* expanded ASCs intra-articular injection (3,4).

This study reports the clinical results of knee OA treatment with *in vitro* expanded ASCs. We think that the selection of the patients based on Kellgren Lawrence grades II and III OA is the right choice since these patients can benefit of this treatment, delaying the time to surgical intervention of knee prosthesis as much as possible. In our experience the ASC infusion was previously shown to be most beneficial for this group of patients (2). A critical point in the patients' eligibility criteria is the enrollment in the study of patients with unstable knees, which in our experience represents a potential contraindication. Patients affected by unstable knees or major axial deviation of the knee were the poorest responders in our series. We think that these patients might have a self-sustained inflammation more difficult to turn off. Moreover, we observed that when patients' knees were washed with a saline solution before cell infusion the outcome was better than in non-pre-washed ones. Thus, the authors should consider the presence of effusion of the knee as a possible hinderance against ASC cell adhesion *in vivo* (5).

According to the authors, we believe that, despite the lack of a formal control/placebo, the results reported should be considered as a pilot study, and further research with more patients should be planned. The obtained results compared to untreated and to pre-operative evaluation suggest a decrease in symptoms and a better performance compared to the classical studies on the placebo effect with a sham knee arthroscopy (6). The real question to be challenged will be how long this procedure is going to be beneficial for the patients. Is this procedure able to revert a progressive primary degenerative OA? Are the injected ASCs directly responsible for regeneration? About this, recent literature infers that the beneficial effect of MSC infusion might be due to the indirect effect of the cell mediated interaction with local actors (chondrocytes and precursors, immune competent cells, etc.), either via direct cell to cell contact or via factors released locally (7,8). One of the major results of the ASC infusion is the inactivation of an inflammatory, self-sustaining phenomenon and not to the reconstruction of a novel cartilage layer (8). Moreover, *in vivo* studies in mouse OA models showed that autologous mesenchymal stem cells (MSCs) disappear from the injected joint in the early phases and that their beneficial effect might be due to an imprinting more than to the continuous presence of the MSCs (9). We believe that the biological composition

of the infused material is a major issue for future research in this field: understanding whether the treatment with expanded ASCs or SVF is better is fundamental for clinical practice. The role of the various precursors, lymphocytes and especially of the factors secreted by the infused cells is relevant for fully understanding the mechanism of action of the regenerative process and to select the active players leading to the relevant clinical results described. Further studies should be issued on this topic as well.

Another particularly relevant aspect is the number of ASC infusion procedures, that should be effective. Indeed, this point acquires great interests for the future therapeutic developments. The authors provided data on the multiple infusion group which are not convincing for its beneficial effect in the long term compared to single infusion, even though MRI showed evidence of a measurable decrease in cartilage loss only in the two-injection group. In more general terms, at 1 year follow up the results of the single infusion are comparable to the ones obtained after two infusions. Moreover, the authors state that a third group, receiving 5 injections, was discontinued due to complications which are not fully described. Thus, some questions should be addressed, such as: "is one infusion enough to obtain long-term results in the reversion of knee OA?" "Are further infusions beneficial in the long-term evolution of the disease, considering that one infusion obtains clinically relevant results maintained after one year from the procedure?" "Are we expecting complications after multiple infusions even though programmed on a yearly basis?"

To evaluate the effect of ASCs in the treatment of knee OA, the other major issue is the quantification of the regenerating effect on the affected cartilage using MRI. Many publications addressed this question without producing convincing information (10,11), due to technical reasons, such as the low resolution of the MRIs available to date or to the necessity of a longer observation periods to visualize the effect. Here, authors reported encouraging results where MRI serial studies showed a reduction or reversion of cartilage loss, but no clear evidence on a cartilage tissue improvement was documented with the methods used [MRI Osteoarthritis Knee Score (MOAKS)]. The author mention further studies to be performed on the quality of the cartilage using T2 mapping techniques, and we can say that we used this technique, without statistically relevant results in our studies (2). The indirect data obtained by MRI imaging such as periarticular bone marrow tissue quality, osteophytes, synovitis, meniscus, periarticular features such as cysts, etc., were not relevantly modified after MSC treatment.

In contrast to clinical data, cell manufacturing process has been briefly described, thus we think that it should be useful to insert more details about the method adopted to obtain 100×10^6 ASCs necessary for the intra-articular injection. Indeed, this is a high number of ASCs and it is not so easy to expand them into two *in vitro* passages only, as described by the authors. Moreover, what parameters were tested by the authors to evaluate the chondrogenic ability of the fresh and thawed ASCs *in vitro*? Could the cryopreservation process modify the differentiation ability of expanded ASCs? We previously demonstrated that cryopreservation of adipose tissue with dimethyl sulfoxide (DMSO) preserves the content of ASCs and their differentiating abilities (12), thus we are confident that also expanded ASCs of this study maintain their properties.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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