Efficacy of a single intra-articular injection of autologous adipose tissue enriched in stromal vascular fraction for the management of symptomatic knee osteoarthritis: tracking data from a retrospective study

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Background
Osteoarthritis (OA), is a disabling joint disorder characterized by articular cartilage degeneration and inflammation (Martel-Pelletier, 2016). Disease symptoms include pain, stiffness and impaired function with a resulting major negative impact on daily activities and patient’s quality of life. (Lane, 2011; Xie, 2016; Cross, 2014). At present, no curative therapy exists and treatment options are aimed at managing symptoms and restore function (Altman, 1998; Jordan, 2003; Zhang, 2007, 2008, 2010;a; Mc Alindon et al., 2014).

Over the last two decades, therapies involving intra-articular injection of autologous cell-derived preparations have gained increasing attention (Di Matteo, 2019, Ha, 2019). Intra-articular administration of those preparations aims to enrich the degenerated cartilage with mesenchymal cells possibly able to differentiating into tissue-specific, regenerating cell populations and/or secrete anti-inflammatory and pro-regenerative growth factors able to interact with the tissue microenvironment (Shi, 2017; Delanois, 2019).

Adipose-derived stem/stromal cells (ADSCs) have been widely investigated as source of mesenchymal stem cells (MSCs) (Bora, 2017; Rannmuthu, 2018; Di Matteo, 2019b). When extracted from adipose tissue by enzymatic digestion, they are contained in an aqueous fraction, known as the stromal vascular fraction (SVF), which contains endothelial precursor and differentiated cells, macrophages, smooth muscle cells, lymphocytes, pericytes, pre-adipocytes and growth factors (Nguyen, 2016; Guo, 2016; Bora, 2017; Pak, 2018). Both ADSCs and SVF have been used in the field of regenerative and reconstructive medicine, with some preliminary evidences of the superiority of SVF (Bora, 2017). Intra-articular injection of adipose tissue has been proven to be effective and safe for the treatment of knee OA in a series of clinical trials (Fodor, 2015; Arturs, 2018; Cattaneo, 2018; Hudetz, 2017; Kim, 2016; Russo, 2017). Traditional separation of SVF from adipose tissue requires extensive tissue manipulation (enzymatic digestion, cell expansion) and dedicated facilities and personnel, thus limiting the use of SVF in the clinical setting (Bora, 2017; Pak, 2018). A system for the preparation of adipose tissue enriched in SVF (at-SVF) within a single surgical session, enzyme-free and with minimal manipulation has been recently developed (Hy-tissue SVF Separation System, Fidia Farmaceutici S.p.A., Abano Terme, Italy). At present, evidence concerning at-SVF effectiveness is limited to a randomized controlled clinical trial with a 6-month follow-up for the treatment of Achilles tendinopathy (Usuelli, 2018).

The present retrospective study aims to assess the efficacy and safety of a single intra-articular injection of at-SVF, prepared using the Hy-tissue SVF system, for the management of knee OA symptoms over a 6-month period.

Methods
Data from 25 subsequent patients aged 25 to 85 years, with a documented diagnosis of knee OA K-L grade II-III, who received an intra-articular injection of at-SVF were collected in a suitable database and analysed. Clinical assessment were performed at 1, 3 and 6 months after treatment according the center’s standard clinical practice. The investigation involved a single center in Italy (Clinica Montallegro, Genova, IT). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki, Good Clinical Practices International Conference on Harmonisation (ICH) Guidelines as well as the principles outlined in the European Regulation UE 2016/679 (GDPR) concerning protection of personal data.

Study Objectives
The primary objective of the present retrospective observational study was to evaluate the benefits of intra-articular injection of adipose tissue enriched in SVF on pain due to knee osteoarthritis (OA) up to 6 months (WOMAC pain (A) subscale). Secondary objectives were:
- To evaluate the benefits of intra-articular injection of adipose tissue enriched in SVF on pain due to knee osteoarthritis (OA) up to 6 months (WOMAC pain (A) subscale).
- To evaluate the local tolerability and safety of intra-articular injection of adipose tissue enriched in SVF up to 6 months.

Results
Complete baseline patient characteristics are summarized in Table 1.

Discussion
The primary objective of the present retrospective study was to evaluate the effect of a single intra-articular injection of at-SVF on pain reduction. Compared to baseline values, patients reported a significant relief from pain even after the first month from the treatment and the amelioration increased over time. Pain reduction was clinically and statistically significant at all study timepoints, with a 56.4% reduction at 1 month, 84.0% at 3 months and 100% at 6 months. Interestingly, a greater improvement was observed for patients experiencing higher pain values at baseline.

The secondary objectives of this investigation aimed to evaluate the benefits of a single at-SVF injection on stiffness and physical function and to assess local tolerability and safety of the treatment. A significant improvement over baseline scores could be observed in all WOMAC sub-scores at 1 month after the treatment, proving the efficacy in the short-term of the intra-articular injection of at-SVF on OA symptoms. Additionally, not only the improvement was maintained for the whole duration of the study but it increased overtime, confirming a durable effect of the treatment up to 6 months.

The presence of crepitus on motion and effusion recorded at baseline were resolved after one month from the injection. No concomitant medication were registered throughout the follow up. No adverse event were recorded. Taken together these results suggested that the treatment had good tolerability and safety.

Conclusions
This retrospective study provides the first evidence of the effectiveness of a single intra-articular injection of at-SVF for the management of symptomatic knee OA. The treatment was shown effective in pain reduction and restoring function, resulting in total symptoms resolution with excellent tolerability and safety. Clinically significant results could be observed at early timepoints and further increased over time. Future studies should be aimed at investigating if such results are long-lasting, and when or if patients should be subjected to further at-SVF injections.

These preliminary results suggest that at-SVF is effective in the reduction of signs and symptoms associated with knee OA and that could be a promising treatment for this disease.