Letter to the Editor

Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis—reply

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Thank you for the constructive editorial commentary on our recently published trial "*Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial*" (1,2).

We agree with the editorial authors' opinion regarding mild to moderate grade osteoarthritis (OA)—Kellgren Lawrence Grade II and III—being a suitable patient population for consideration of treatment. With an increasing proportion of patients undergoing total knee replacement surgery under the age of 65 and with an anticipated significant increase in the number of total knee replacement being performed, it is important to consider how we can best delay or prevent unnecessary surgery (3,4).

The editorial authors have considered knee instability and major axial deviation as potential mechanical contra-indications to mesenchymal stem cell (MSC) therapy. Whilst the study excluded patients with a long leg mechanical axis >5 degrees, ligament deficiency was not a specified exclusion criterion. Review of the participant population, however, showed no history of clinically significant instability with a single patient having had a history of anterior cruciate ligament (ACL) reconstruction. We agree, however, that gross instability may limit potential benefit due to repetitive chondral trauma. The editorial authors also raise an interesting consideration that the presence of effusion may be a potential hindrance to MSC adhesion. Whilst, not part of the trial protocol we would agree that aspiration of effusion prior to MSC intra-articular injection is appropriate.

The lack of formal placebo/sham injection is noted and is an accepted limitation of the trial. It was felt inappropriate to perform an invasive lipo-harvest procedure if participants were to be randomly allocated to the control group and not receive active therapy. Importantly, as the editorial authors have noted, the effect size observed in both pain and function following MSC therapy is greater than that observed in other placebo controlled intra-articular therapies and also in comparison to the observed placebo effect with sham knee arthroscopy (5,6).

Due to lack of previous formal trials in this area we were not able to perform sample size power calculations to determine an appropriate trial participant number. Retrospective power calculations for all statistical tests performed for pain and functional outcome measures did, however, show excellent consistency (mean power score of 0.877) confirming that despite the small participant population the results were reproducible and participant numbers were appropriate to show statistical significance. We do however accept that a broader study with greater numbers is important with perhaps less restrictive inclusion/exclusion criteria to better represent the general patient population.

The editorial authors have raised the question of mechanism of action attributable to MSC therapy. We agree that the likely mechanism of action is via paracrine mechanisms and cell to cell interaction (7,8). Preclinical

trials have shown MSC retention at 6 months after intra-articular injection to be 1.5% (9). We theorize that long term benefit is likely due to exosomal release of not only relevant cytokines but also mRNA which is taken up by local cells resulting in up-regulation of cellular pathways and long term imprinting of benefits.

As the editorial authors correctly point out, our trial involves the use of isolated and expanded adipose derived MSCs and not stromal vascular fraction (SVF). During the design of this study, it was felt that past pre-clinical and clinical research had more consistently shown the potential benefit of isolated and expanded MSC therapy to result in disease modification (10-12). Adipose tissue was chosen rather than bone marrow as a source of MSCs due to ease of harvest and relative abundance of MSCs. Comparative studies using SVF have been limited in design and whilst indicating pain and functional improvement, structural benefits are less consistently reported (13,14). In addition to this, the number of MSCs found within SVF differs dramatically with anticipated variability in outcome due to inconsistency in the cell dose.

As noted in the editorial, a third treatment group receiving 5 injections at regular intervals was planned but ceased prior to commencement of the trial due to a parallel trial with this same protocol showing reproducible and increasing pain with sequential injections. The second injection of MSC therapy at 6 months in the two injection group was associated with a modest increase in reported pain in comparison to the initial injection. Importantly the two injection group showed greatest consistency in disease modification with stabilization and/or cartilage improvement in 89% of participants within this group versus 70% of participants in the single injection group. These results indicate that multiple injections may achieve better structural stabilization but as the editorial authors correctly note this may be associated with increased adverse events and we have yet to strongly determine the most effective treatment frequency for long term efficacy and tolerability.

As the editorial authors note, and as noted by ourselves, the MRI analysis in this trial is limited in that MRI Osteoarthritis Knee Score (MOAKS) is a semi-quantitative measure. MRI T2 mapping techniques are a non-invasive and validated assessment of cartilage quality and in combination with cartilage volume assessment may offer more precise and robust quantitative structural assessment and conclusions (15,16).

The editorial authors have requested additional information regarding the processes used in adipose-derived MSC preparation. The method of preparation has been previously described in past publications including a protocol paper and it was felt that the description given met the appropriate minimum level of information required for studies evaluating biologics in orthopaedics (MIBO) (17).

This trial represents the first randomized controlled trial on the use of isolated and expanded adipose-derived MSCs in the treatment of OA. Importantly the significant pain and functional improvement and observed disease modification indicate that MSC therapy represents an exciting advancement in the treatment of OA.

Acknowledgments

None.

Footnote

Conflicts of Interest: J Freitag is associated with Magellan Stem Cells and a member of its Medical and Scientific Advisory Committee.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Freitag J, Bates D, Wickham J, et al. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. Regen Med 2019;14:213-30.
2. Roato I, Ferracini R. Is the adipose-derived mesenchymal stem cell therapy effective for treatment of knee osteoarthritis? Ann Transl Med 2019;7:S114.
3. Knutson K, Robertsson O. The Swedish knee arthroplasty register. Acta Orthop 2010;81:5-7 .
4. Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780-5.
5. Bar-Or D, Rael LT, Brody EN. Use of saline as a placebo in intra-articular injections in osteoarthritis: potential contributions to nociceptive pain relief. Open Rheumatol J 2017;11:16-22.
6. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee.

N Engl J Med 2002;347:81-8.
7. Caplan AI. Why are MSCs therapeutic? New data: new insight. J Pathol 2009;217:318-24.
8. Mancuso P, Raman S, Glynn A, et al. Mesenchymal stem cell therapy for osteoarthritis: the critical role of the cell secretome. Front Bioeng Biotechnol 2019;7:9.
9. Toupet K, Maumus M, Peyrafitte JA, et al. Long-term detection of human adipose-derived mesenchymal stem cells after intraarticular injection in SCID mice. Arthritis Rheum 2013;65:1786-94.
10. Lee KB, Hui JH, Song IC, et al. Injectable mesenchymal stem cell therapy for large cartilage defects--a porcine model. Stem Cells 2007;25:2964-71.
11. Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. Stem Cells 2014;32:1254-66.
12. Vega A, Martín-Ferrero MA, Del Canto F, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. Transplantation 2015;99:1681-90.
13. Fodor PB, Paulseth SG. Adipose derived stromal cell (ADSC) injections for pain management of osteoarthritis in the human knee joint. Aesthet Surg J 2016;36:229-36.
14. Roato I, Belisario DC, Compagno M, et al. Concentrated adipose tissue infusion for the treatment of knee osteoarthritis: clinical and histological observations. Int Orthop 2019;43:15-23.
15. Baum T, Joseph GB, Karampinos DC, et al. Cartilage and meniscal T2 relaxation time as non-invasive biomarker for knee osteoarthritis and cartilage repair procedures. Osteoarthritis Cartilage 2013;21:1474-84.
16. Cicuttini F, Forbes A, Asbeutah A, et al. Comparison and reproducibility of fast and conventional spoiled gradient-echo magnetic resonance sequences in the determination of knee cartilage volume. J Orthop Res 2000;18:580-4.
17. Murray IR, Geeslin AG, Goudie EB, et al. Minimum information for studies evaluating biologics in orthopaedics (MIBO): platelet-rich plasma and mesenchymal stem cells. J Bone Joint Surg Am 2017;99:809-19.

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