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Therapy with mesenchymal stem cell transplantation in multiple sclerosis ready for prime time: Commentary

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This edition of *Controversies* asked us to consider whether we have sufficient evidence to support the wider use of cell-based therapies with mesenchymal stem cells (MSCs) for people with multiple sclerosis (pwMS).

Convincing data support the feasibility and safety of the injection of autologous MSCs for pwMS, with no life-threatening or serious adverse events detected so far. This comes irrespective of how MSCs are defined and cultured in independent facilities,[1] whether MSCs obtained from pwMS may be 'deficient'[2] and how the final cellular product is delivered. Nonetheless, the efficacy of autologous MSC therapeutics is still a cause of conflicting positions, as most studies have been limited to phase I/II, strong positive outcomes are still hit-and-miss and comparing results from different trials is challenging. Therefore, the two opposing views published in this issue of the *Multiple Sclerosis Journal* try to provide key efficacy data to guide us in the understanding of whether MSCs for pwMS are finally ready for *prime time*.

On the 'YES' side of this controversy, Drs. Karussis, Kassis, and Petrou focus on data from their own studies, including a randomised double-blind controlled trial on progressive multiple sclerosis (MS) that shows that the intrathecal (IT) delivery of MSCs is superior to sham and intravenous (IV) MSC injections.[3] Despite that these data fit with the growing idea that targeting central nervous system (CNS)-compartmentalised inflammation in progressive MS could be key to treat this phase of disease, this study presents key limitations. These include the relatively small number of patients enrolled, its short duration and the evidence of severe clinical progression before treatment in half of the patients leading to a possible 'regression to the mean' interpretation bias.[3] Interestingly, a follow-up study performed a correlative analysis of cerebrospinal fluid (CSF) biomarkers of inflammation and neurodegeneration from the same cohort of patients.[4] IT MSCs reduced the levels of neurofilament-light chain (NF-L) – but not those of CXCL13 – in the CSF at 6 months post-treatment. However, the NF-L levels were not significantly different from those in the IV MSCs or sham-treated groups. The results of an open prospective study designed to evaluate the long-term clinical and immunological effects of multiple (IT + IV) MSC injections in people with active progressive MS were also encouraging.[5] However, these data were tarnished by the fact that only a minority of the patients (7/24) was able to reach and complete the 48 months endpoint, thus making hard to believe the overemphasised neuroprotective effects of MSC therapeutics in pwMS.

On the 'NO' side, Drs. Uccelli and Freedman mostly focus on the results of MESEMS, the largest investigator-initiated, randomised, double-blind, placebo-compared phase II study of MSCs in MS.[6] MEsenchymal StEm cells for Multiple Sclerosis (MESEMS) concluded that a single IV dose of autologous MSCs has no effect on MS disease activity, *de facto* providing a final answer to whether MSCs

should be used in pwMS.[6] However, the MESEMS has missed the chance to provide a definitive conclusion to this matter for several reasons. First, MESEMS failed to rule out the possibility that an arbitrary dose of systemically injected $1–2 \times 10^6$ autologous MSC/kg body weight is just not enough to achieve significant efficacy outcomes in subjects with active MS. Second, MESEMS did not investigate routes of cell delivery besides the IV injection, leaving other routes as unexplored options to be investigated in following large clinical trials. Third, MESEM had a clear issue of patient selection and it missed the opportunity to fully focus on early progressive (or transitional) MS patients. In fact, MSCs compete in a market fully dominated by highly effective disease-modifying treatments (DMTs), which have shown far greater and consistent therapeutic effects in people with relapsing remitting MS. Therefore, focusing on progressive MS patients via dedicated dose-escalation studies (vs gold standards of care) must be a priority.[7] Unfortunately, the way MESEMS was designed did not allow to specifically address the above key points, leaving us to wonder '*what if?*'.

Common to several cell secretome therapeutics,[8] the lack of a single and predominant mechanism of action exerted by MSCs has led to shortcomings in trial design, prospective identification of biomarkers of efficacy and ultimately the whole *druggability* of MSCs. In addition, current health economics data suggest that the costs of autologous MSCs are still overpowering their potential therapeutic effects.[9] While this unbalance may be resolved if MSCs will become more widely adopted, the *high-cost high-safety* profile of MSCs has led to the flourishing of biotech companies that supply unproven MSC therapies as a paid treatment for MS.[10] In summary, having discussed both commentaries, it appears clear that autologous MSCs for pwMS are *NOT* ready for prime time, at least *NOT YET*. As such, we still must rely on current rigorous basic mechanistic research and next MS (NCT04749667, NCT05003388, NCT05116540, and NCT04956744) and non-MS clinical trials (including those with allogeneic MSCs) to address the plethora of questions that are still open in this exciting field.

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