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A Meta-analysis of the use of mesenchymal stem cells in the treatment of multiple sclerosis – lack of clinical efficacy through insufficient cell numbers administered?

MS is a chronic and progressive neurodegenerative disease affecting 100,000 in the UK. Its exact cause remains unknown but autoimmunity is considered to play a role in the destruction of myelin sheath of neurons, leading to disturbances in vision, weakness, acute and chronic pain, fatigue and paralysis. Current therapy involves immunomodulators. However, despite significant improvements in patient survival and debility, these therapies are not fully effective in slowing disease progression. Much of this is due to neurodegeneration which is not corrected by these therapies. Mesenchymal stem cells (MSC) are nonhaemapoetic stromal cells which have multipotentiality, immunomodulatory and paracrine properties which it is hypothesised may be exploited to repair and reduce axonal demyelination associated with MS. MSCs are easily expanded, have a safe infusion profile and can be used autologously (Harris *et al*., 2012). All CTs so far have been safety and pilot trials, so a meta-analysis has been carried out to assess the efficacy of MSC transplantation in the treatment of MS.

All MS CTs involving autologous MSCs administered by any route (i.v. or intrathecal) were searched via Clinicaltrials.gov, Pub Med, Cochrane Centre, Science Direct, Royal Society of Medicine, and PLOS.org up to April 2015. The outcome chosen was the Kurtzke Extended Disability Status Scale (EDSS) before and after treatment. This uses a functional system score (0-10) for 8 systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other (Kurtzke, 1983). analysis was performed using Revman 5.3 (Copenhagen, Nordic Cochrane Centre, 2012).

Clinicaltrials.gov elicited 21 results, of which only 3 were completed, and only 1 published (Connick et al., 2011). The other databases elicited a total of 246 results. Of these 10 trials were identified as being of interest. 5 were excluded as being observational, did not report EDSS as an outcome, or were abstracts that did not include sufficient quatitative data. One trial only included baseline EDSS data and was excluded (Connick et al., 2011). The remaining 4 trials (Bonab et al., 2012; Karussis et al., 2012; Yamout et al., 2010; Bonab et al., 2007) yielded a total of 59 patients with follow-up between 6-12 months.

Mean fixed effect EDSS before treatment was (mean±SD) 6.5±1.17 and after treatment 6.34±1.21, with a mean difference (95%CI) of 0.08(-0.18-0.35), Z=0.62, p=0.54. Heterogeneity I^2=46%. Two of the four trials produced improved scores, whilst the other two elicited an increase in disability. A sub analysis revealed that the numbers of cells administered were important. Taking the trials of Bonab et al. (2010), Bonab et al. (2010), and Yamout et al, 2010), % reduction in MS lesions as determined by MRI over baseline was 4.5% ($2.5x10^6$ cells), 10.0% ($8.7x10^6$) and 28% ($49.0x10^6$).

There were a limited number of trials that included EDSS as an endpoint. Whilst many included MRI outputs, few were associated with clinical outcomes that quantified patient improvement. Of the limited number seen, it is clear that the numbers of cell administered is important, and that future trials should take this into consideration.

Bonab, et al., (2007). *Iran J Immunol.* 4: 50-57.

Bonab, et al., (2012) *Curr Stem Cell Res Ther*. 7: 407-414.

Connick, P. et al., (2011) *Trials.* 12(62).

Karussis, et al., (2006*) Clin Neurol Neurosurg. 108.* 250-4.

Yamout, B., et al., (2010) *J Neuroimmunol.* 227(2). pp.185-189.