COMMENTARIES

Mesenchymal Stem Cells and Neurodegenerative Disease

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The prospect of cell therapy for incurable neurodegenerative disease excites scientists, the public, and patients alike. Clinical and scientific enthusiasm must, however, always be tempered by methodological rigor and by the overwhelming imperative of protecting vulnerable sufferers. We tentatively suggest that, in the case of autologous mesenchymal stem cells (MSCs), the balance between our current understanding of their biology and an informed assessment of their probable safety allows a case to be made for cautious pilot clinical studies.

Quinn and colleagues, commenting on the recent safety and feasibility study of autologous MSC therapy in individuals with multiple system atrophy (MSA),[1] make a number of invaluable and timely points concerning the premature introduction of stem cell therapies.[2] They rightly draw attention to the need for very great caution in advancing or inferring efficacy from a single, small, uncontrolled phase I study; they allude to important questions about the potential hazards of intra-arterial cell delivery; and they hint that such clinical studies may be premature. We wholeheartedly endorse their conclusion that, at present, there is "little scientific justification for their clinical *use* [our emphasis] in neurodegenerative conditions."

They might have added that the uninhibited claims of clinical benefit made in such studies (not least following their appearance in a highly influential journal) will doubtless be exploited by the numerous outfits around the globe currently preying on vulnerable patients by the direct-to-sufferers sale of so-called stem cell therapies of no proven value at great price and profit.[3]

But would it be right to conclude that such feasibility studies should not be performed at all, or only that they should be meticulously designed and properly interpreted? Although, as Quinn and colleagues suggest, larger comparable studies using intra-arterial delivery in MSA may not yet be justified, and certainly not widespread clinical use, we suggest that recent advances in our understanding of the biology of MSCs allow a case to be made for small-scale studies beginning to explore the potential of autologous, intravenously delivered MSCs in neurodegenerative disease.

Quinn *et al.* rightly point out that research five or more years ago showing that MSCs could fuse *in vitro* with other cell types was widely interpreted as indicating that the therapeutic potential of adult stem cells might be very limited.[4] Others at that time, however, suggested the opposite—that fusion might represent a means by which MSCs could "rescue" damaged or effete cells and so help tissue repair.[5] Over the next few years it became clear that cell fusion was indeed one mechanism by which MSCs could deliver therapeutic benefit[6]—but that in other experimental circumstances true transdifferentiation, not fusion, seemed a more likely explanation.

Furthermore, other mechanisms by which MSCs could contribute to tissue repair, including significant immunity-modulating properties, vasculogenic effects, and (especially important in the current context) the release of neurotrophic factors, were subsequently revealed.[7] It has become clear that transdifferentiation is but one of many potentially therapeutic properties of adult stem cells[8]—and quite possibly not the most important. Furthermore, stem cells from developing tissue also act beneficially (in experimental neurodegenerative disease) through multiple mechanisms, with only a "small degree of neuronal replacement."[9] The early, near-unanimous emphasis on transdifferentiation to replace cells as the key to cell therapy is, arguably, proving an insufficiently subtle approach to the complexities of both spontaneous and therapeutic tissue regeneration and repair.

More recently, fusion of adult stem cells has received further experimental attention. It has been confirmed that bone marrow–derived cells can contribute to differentiated cell populations in various tissues—including cerebellar Purkinje cells (of particular relevance, of course, to MSA)—through the formation of stable reprogrammed fusion hybrids.[10,11] This is triggered by injury and, especially, inflammation, strongly suggesting a reparative (or "rejuvenating") effect of obvious therapeutic potential.[12]

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Finally, autopsy studies of persons many years after receiving sex-mismatched bone marrow transplants (for blood disorders) reveal small numbers of apparently fully integrated and functional cells of highly specialized morphology in a variety of organs—again, including cerebellar Purkinje cells—whose nuclei are clearly of donor origin.[13,14] These findings lend strong support to the reparative potential of bone marrow–derived cells (delivered intravenously in these instances, of course).

A glance outside neurological medicine to cardiology may also be informative. Here, a more accelerated pace of investigating the possible clinical benefits of MSCs has been apparent. A recent authoritative review considered more than 30 clinical trials in both acute and chronic heart disease, and the authors already felt able to conclude that "mesenchymal stem cells…can, under appropriate conditions in select patients, provide disease-ameliorating effects in…cardiovascular disorders."[15] Significantly, however, the precise mechanism(s) by which the cells exerted this benefit remain unclear.

We therefore believe that there are, however limited, clear experimental reasons to believe that autologous MSCs could be of benefit in neurodegenerative disease. There are few, if any, reasons to fear that such cells are intrinsically likely to have adverse effects. Although the balance of evidence may arguably not be sufficient to overcome the hazards of intra-arterial or, more obviously, intracerebral implantation, intravenous delivery is very likely to be harmless, and indeed cardiological and extensive other clinical experience supports that likelihood. It is absolutely vital, of course, to continue the further investigation of MSCs and their basic and applied biological properties, but, in light of the above progress, we believe that, in progressive and untreatable neurodegenerative diseases such as MSA, a case can be made for cautious pilot clinical studies.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Safety Issues of Maternal Drug Therapy During Breastfeeding

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Two goals when counseling breastfeeding mothers taking medication are protecting the infant from adverse events and permitting necessary maternal therapy. Madadi *et al.* report a case–control study of neonatal and maternal opioid toxicity after codeine administration. Therapeutic considerations in counseling breastfeeding mothers include susceptibility to drug toxicity of the very young and/or premature infant, significant interindividual variations in drug response, the dose–response relationship with respect to drug toxicity, and the role of pharmacogenetics in both the mother and the infant. These host factors may combine in a particular patient to act synergistically to produce an adverse reaction.

The best nutrition for infants entails exclusive breastfeeding for the first 6 months of life and human milk as the sole source of milk throughout the first year of life.[2] Accordingly, many organizations worldwide have emphasized the importance of breastfeeding. As a result, the percentage of infants ever breastfed in the United States has steadily increased from 60% in 1993–1994 to 77% in 2005–2006 (ref. 3). This latter figure now exceeds the US Department of Health and Human

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