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Dr Rahimi-Movaghar raises several important issues when considering cell transplantation therapies in spinal cord injuries, particularly when considering “the next steps” in olfactory ensheathing cell transplantation. The animal model data continue to indicate efficacy for these cells, so what is the logical next step in taking them through the clinical trial process? Our first study was a Phase I design with aspects of Phase II, namely a single blind study with an un-operated control group and blinded assessors (Mackay-Sim et al, 2008). One logical progression is to repeat the trial with a larger cohort. Our first trial had group sizes of three, chosen because the risk was unknown. Clearly a larger number is required to be totally confident that the procedure is safe. Another logical progression is to move to a Phase II trial design to examine efficacy. A large, Phase II trial design with staggered entry may fulfil requirement for further testing of both the safety and efficacy.

The next part of the decision process is to decide the location of injury. As we discussed (Mackay-Sim et al, 2008) and as considered by Rahimi-Movaghar, thoracic injuries minimise the risk of functional impairment, should the procedure prove damaging. This is considered optimal for safety trials (Tuszynski et al, 2007). Alternately, thoracic injuries are severe, particularly those leading to complete paraplegia, making any repair task much the greater. This is sub-optimal for observing any efficacy of treatment. Additionally occurrence of thoracic is less frequent adding to recruitment difficulties. Maybe the task will be too hard. These constraints suggest that one should next choose a site of injury that may have a good chance of observing functional recovery, while keeping the risk of treatment low. We agree with Rahimi-Movaghar that injuries lower or higher in the cord than we chose would have a better probability of observing functional changes. Risk may be reduced by transplanting cells into the injury and the cord below, but not above, the injury.

As noted (Fawcett et al, 2007), there is a finite chance of natural recovery after any spinal cord injury, a chance that is highest initially and higher for incomplete compared to complete injuries. While early, incomplete injuries may be expected to benefit most from cell transplantation (or other therapies), natural recovery makes it much more difficult to assign functional changes due to treatment. Therefore the numbers of trial participants (and cost) conflates with the severity of injury (incomplete or complete) and the time of treatment (period since injury).

Consider too, that efficacy trials also require controls with blinded assessors to control for potential biases that are magnified by the largely clinical nature of the assessment of functional recovery. This lack of controls and blinded, independent assessment significantly reduces the value of evidence generated by recent applications of olfactory mucosal transplantation and fetal olfactory bulb cells (Lima et al, 2006; Huang et al, 2003; 2006).

Rehabilitation in concert with cell transplantation is a hot topic in the field. There is some evidence that rehabilitation alone can be beneficial after human spinal cord injury (Harvey et al, 2008; Harness et al, 2008) and a tailored rehabilitation regime augmented recovery after olfactory ensheathing cell transplantation for spinal cord injury in rat (Kubasak et al, 2008). In other human trials of olfactory tissues (Lima et al, 2006; Huang et al, 2006) and of Schwann cells (Saberi et al, 2008) all patients underwent exercise or other forms of rehabilitation. In those studies there was no formal test of rehabilitation such that there was no control group for rehabilitation just as there was no control group for cell transplantation. This complicates interpretation of outcomes which would have confounded cell transplantation with rehabilitation. In practice, adding a “rehabilitation” arm to a cell transplantation study greatly increases the complexity of the trial, the more so at this stage when efficacy of cell transplantation alone has not been demonstrated. There is also the issue of the actual rehabilitation program that may be incorporated. The optimal type, components and intensity of rehabilitation or exercise therapy needs to be ascertained for different severities and levels of injury. While it may be logical to assume that the addition of “rehabilitation” to a cell

transplantation therapy would be of benefit, the practicalities of incorporating it into a clinical trial should not be under-estimated.

Rahimi-Movaghar states that neurological assessments should be made daily for one week following cell transplantation. It is not clear exactly why this time period is recommended. In our trial the first neurological assessment was performed by the Reviewing Physician at 10 days post-surgery. The first signs of recovery in the single patient were recorded at 3 months. Contrary to the suggestion by Rahimi-Mavaghar this was not reported at one year (Feron et al, 2005) in order to maintain the blinding necessary for the success of the trial over 3 years.

References

Féron F, Perry C, Cochrane J, Licina P, Nowitzke A, Urquhart S, Geraghty T, Mackay-Sim A. Autologous olfactory ensheathing cell transplantation in human spinal cord injury. Brain. 2005;128: 2951-60.

Harness ET, Yozbatiran N, Cramer SC. Effects of intense exercise in chronic spinal cord injury. Spinal Cord. 2008; Jun 3. [Epub ahead of print]

Harvey LA, Lin CW, Glinsky JV, De Wolf A. The effectiveness of physical interventions for people with spinal cord injuries: a systematic review. Spinal Cord. 2008; Aug 26. [Epub ahead of print]

Huang H, Wang H, Chen L, Gu Z, Zhang J, Zhang F, et al. Influence factors for functional improvement after olfactory ensheathing cell transplantation for chronic spinal cord injury. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2006; 20: 434–8.

Kubasak MD, Jindrich DL, Zhong H, Takeoka A, McFarland KC, Muñoz-Quiles C, Roy RR, Edgerton VR, Ramón-Cueto A, Phelps PE. OEG implantation and step training enhance hindlimb-stepping ability in adult spinal transected rats. Brain. 2008;131: 264-76.

Lima C, Pratas-Vital J, Escada P, Hasse-Ferreira A, Capucho C, Peduzzi JD. Olfactory mucosa autografts in human spinal cord injury: a pilot clinical study. J Spinal Cord Med. 2006; 29: 191-203; discussion 204-6.

Mackay-Sim A, Féron F, Cochrane J, Bassingthwaighte L, Bayliss C, Davies W, Fronek P, Gray C, Kerr G, Licina P, Nowitzke A, Perry C, Silburn PA, Urquhart S, Geraghty T. Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3-year clinical trial. Brain. 2008; 131: 2376-86.

Saberi H, Moshayedi P, Aghayan HR, Arjmand B, Hosseini SK, Emami-Razavi SH, Rahimi-Movaghar V, Raza M, Firouzi M. Treatment of chronic thoracic spinal cord injury patients with autologous Schwann cell transplantation: an interim report on safety considerations and possible outcomes. Neurosci Lett. 2008; 26: 46-50.

Alan Mackay-Sim