President: Prof Richard Macdonell
Honorary Secretary: A/Prof Helen Dewey
Treasurer: Dr Michelle Kiley

AUSTRALIAN & NEW ZEALAND
ASSOCIATION OF NEUROLOGISTS
ABN 22 007 221 301

2 March 2015

To:
Biological Science Section
Office of Scientific Evaluation
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

bloodandtissues@tga.gov.au

Dear Sir/Madam

Re.:Consultation: Regulation of autologous stem cell therapies: Discussion paper for consultation

As Chair of the MS Neurology Group of the Australian and New Zealand Association of Neurologists (ANZAN) I would like to provide the following in response to the above discussion paper.

As neurologists who treat patients with multiple sclerosis (MS) we have recently become increasingly concerned by the number and variety of clinics that have been offering various forms of stem cell therapy to treat MS. We would concur with the broad range of concerns raised in the discussion paper which we believe covers the major issues comprehensively.

Our major concern is the unregulated offering of stem cell therapies directly to patients with limited data regarding efficacy. An additional general concern is with regards to the potential for patients to be confused by the array of stem cell therapies being offered and the promise of stem cells being regenerative. The nature of our concerns is slightly different between the various therapies and we would like to deal with them separately.

Autologous Haematopoietic Stem Cell Therapy

Autologous Haematopoietic Stem Cell Therapy (AHSCT) or bone marrow transplantation appears in observational and early phase II clinical trials to offer some therapeutic benefit in active, aggressive MS.[1 2] There are indications that patients with progressive, later stage disease do not benefit from this therapy. A phase III trial of bone marrow transplantation for MS has been proposed,[3] and the phase III MIST trial has commenced accrual in USA, England and Singapore (https://clinicaltrials.gov/ct2/show/NCT00273364). The risks of AHSCT are well described and are considerable. One of the largest reviews of observational studies in Europe using current state-of-the-art procedures showed a 100 day procedure related mortality of 2%.[4] The 5 year procedure related mortality was 3.7%.[4] More recent studies suggest the figure may be as low as 1.3%.[5] We therefore feel that this is a therapy that is worth considering for patients who have active disease and have failed other therapies or where other therapies are contraindicated.[6] We would ideally like to see the completion of formal phase III clinical trials but recognise that these will, through necessity, have to be comparator rather than placebo-controlled and single rather than double-blind. A placebo-controlled trial in this group of patients would be unethical and the nature of the treatments means that true blinding of the patient and treating physician would be impossible.

Our primary concern with AHSCT is the need to establish comparative efficacy. At a regulatory/government level this is also important in terms of the cost/benefit analysis of AHSCT in comparison to existing effective therapies such as natalizumab and alemtuzumab.

We are also concerned by the number of patients with mild disease or advanced progressive disease, who may be exposed to unnecessary risk or are unlikely to benefit from this therapy, but are seeking AHSCT overseas at considerable personal cost. We appreciate that the TGA has no jurisdictional control with regards to overseas suppliers of AHSCT.

Mesenchymal and fat-derived stem cell therapies

We have been very alarmed by the number of private practitioners and clinics across Australia and internationally that have been offering mesenchymal and fat-derived stem cell therapy for MS. Such therapies are often offered at very high costs to patients and there is a heavy reliance on personal testimonies and "miracle cure" stories in the advertising used by some clinics. There has also been a worrying trend of clinics offering treatment as part of a "trial" whilst charging for the therapy.

Whilst these therapies appear to be relatively safe, their efficacy is completely unknown.[7] We are not aware of any phase IIb or phase III clinical trial data for mesenchymal stem cell therapy in MS. Further trials of mesenchymal stem cell therapy for MS are under way but have yet to be completed.

Conclusion

We would strongly advocate for Option 5 (Regulate under the Act as Class 2, Class 3 or Class 4 biologicals) as outlined in the discussion document. We believe that this is the only way in which the core issue of establishing efficacy for these treatments can be ensured. We believe that the case for this is stronger for mesenchymal stem cell therapy and fat-derived stem cell therapy in particular. We note that the provision of AHSCT therapy for MS is largely confined to public hospitals and is therefore already constrained by human research ethic committee review and NPAC/NATA accreditation with regards to procedural safety.

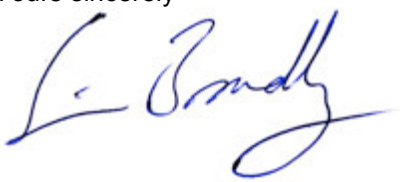
We note that autologous haematopoietic stem cell transplantation for cancer therapy is currently on the Item 4(q) exclusion list. We would be supportive of autoimmune diseases, including MS, being added to this list under point 6 of Appendix 1. This is Option 3 as outlined in the discussion document.

We would add that we would not wish to see a situation where the further development of any effective therapy for MS is hindered. Thus, while calling for regulation of stem cell therapies for MS, we would also recommend consideration of structures that might promote the collection of relevant efficacy and safety data on such therapies in Australia. We appreciate that this may be outside the scope of the TGA discussion document, but mechanisms by which more cost effective, unsponsored registries and clinical trials of non-pharmacological and non-therapeutic device therapies can be conducted.

If you require any further input we would be happy to assist.

The neurologists listed below have all approved the final version of this letter.

Yours sincerely



Professor Simon Broadley

Signatories
Prof Simon Hawke (NSW)
Dr Mark Marriott (VIC)
A/Prof Mark Slee (SA)
A/Prof Jeannette Lechner-Scott (NSW)
A/Prof Helmut Butzkueven (VIC)
Prof Pamela McCombe (QLD)
Prof Allan Kermode (WA)
Prof Bruce Taylor (TAS)
A/Prof Michael Barnett (NSW)
A/Prof Steve Vucic (NSW)
Dr Heidi Beadnall (NSW)
Dr Ann French (VIC)
A/Prof Stephen Reddel (NSW)
Dr Suzanne Hodgkinson (NSW)
Professor Richard Macdonell (VIC)
Professor John Pollard (NSW)
Prof Trevor Kilpatrick (VIC)

With additional review from:
Dr John Moore (Haematologist, St Vincent's Hospital, Sydney)

References

1. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 2012;**47**(6):770-90.
2. Mancardi GL, Sormani MP, Gualandi F, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: A phase II trial. Neurology 2015.
3. Saccardi R, Freedman MS, Sormani MP, et al. A prospective, randomized, controlled trial of autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: a position paper. Mult Scler 2012;**18**(6):825-34.
4. Farge D, Labopin M, Tyndall A, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases. Haematologica 2010;**95**(2):284-92.
5. Radaelli M, Merlini A, Greco R, et al. Autologous bone marrow transplantation for the treatment of multiple sclerosis. Current neurology and neuroscience reports 2014;**14**(9):478.
6. Broadley SA, Barnett MH, Boggild M, et al. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective: part 2 new and emerging therapies and their efficacy. J Clin Neurosci 2014;**21**(11):1847-56.
7. Karussis D, Karageorgiou C, Vaknin-Dembinsky A, et al. Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. Archives of Neurology 2010;**67**(10):1187-94.