RESEARCH AUSTRALIA

Multiple Sclerosis Research Australia
1300 356 467 • info@msra.org.au • www.msra.org.au
level 26, Northpoint 100 Miller Street • North Sydney • NSW 2060
PO Box 625 • North Sydney • NSW 2059
ABN 34 008 581 431

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

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

MS Research Australia would like to thank the TGA for undertaking this timely and important review of the regulations surrounding the provision of autologous stem cell therapies in Australia.

About MS Research Australia

MS Research Australia is the largest national not-for-profit organisation dedicated to funding and coordinating multiple sclerosis research in Australia, as part of the worldwide effort to solve MS. Its goal is to accelerate research into the cause, better treatments and prevention of MS, with the aim of ultimately finding a cure for MS.

MS is the result of damage to myelin – a protective sheath surrounding nerve fibres of the central nervous system. When myelin is damaged, this interferes with messages between the brain and other parts of the body. The symptoms of MS are different for each person; sometimes they even vary within the same person. For some, MS is characterised by periods of relapse and remission, while for others it has a progressive pattern.

A number of disease modifying medications are available for people with the relapsing remitting form of MS. These medications can be very effective in controlling relapses, however, they do not work for everyone and can be accompanied by a range of side-effects and risks.

For people with the progressive forms of MS there are currently no medications with proven efficacy to halt the relentless accumulation of disability.

For these reasons many people with MS seek to explore all possible avenues of treatment open to them. In many cases this search may lead them to investigate the option of unproven stem cell treatments that are provided by clinics within Australia and overseas.

Stem cell treatments for MS

Currently the only stem cell therapy that is currently provided for people with MS via public hospitals within Australia is Autologous Haematopoietic Stem Cell Transplant (AHSCT). This is a form of treatment targeted at resetting the immune system. It is still considered experimental by hospital ethics committees and hospital administrators, as clinical trials and observational studies are currently underway to gather further evidence on its safety and efficacy. As such it is only provided on a case by case basis in a limited number of hospitals

within Australia, for a small percentage of people with severe forms of MS that do not respond to licensed MS therapies. One observational clinical trial is currently underway in an Australian hospital, and MS Research Australia is supporting the MS AHSCT Registry which is gathering data on Australians who have received this therapy.

As pointed out in the TGA's discussion paper (Attachment 1), AHSCT for the treatment of cancer (along with other forms of tissue used in circumstances such as bone and skin grafts) is not included in the current regulatory review. This is an appropriate and important distinction. MS Research Australia would like to suggest that AHSCT for the treatment of certain autoimmune disorders could also be included in the list set out in Attachment 1, along with AHSCT for cancer treatment, where it continues to be provided by experienced hospital centres subject to NPAC/NATA accreditation. This would facilitate the continued assessment of AHSCT as a potential treatment for severe autoimmune disorders.

Mesenchymal stem cells (MSCs) derived from blood, adipose tissue and other sources, are in the early stages of pre-clinical and clinical investigation for the treatment of MS. Other types of stem cells such as neural stem cells and induced pluripotent stem cells are also under investigation, but have yet to advance much beyond the level of laboratory and pre-clinical research. As such, the potential role that MSCs, and other types of stem cells, may play in the range of treatment options available to people with MS is far from clear and their efficacy and safety has yet to be proven.

Provision of unproven 'autologous stem cell' therapies for MS

Despite the current status of progress in stem cell research for MS, MS Research Australia is aware of a number of private clinics within Australia that offer 'stem cell' treatments and include MS as one of the disorders for which treatment is offered. As far as we are aware, the treatment most commonly offered is extraction of fat (adipose) tissue from the patient followed by preparation of a cell extract which is then reinfused into the patient.

This situation is deeply concerning to MS Research Australia. Firstly, because there is no standardised or licensed method for the preparation of the adipose tissue, such that the cell extract that is reinfused is likely to contain a broad mixture of cells, rather than a purified preparation of well-characterised stem cells. Also, as discussed above, it exposes many people with MS to the potential risks of a medical intervention with no evidence for any benefits which may outweigh or justify those risks.

The current exclusion of autologous human cells and tissues from regulation under the Act is intended to cover tissues where they are: i) for use in the patient from which they were taken; 2) used under the supervision of a medical practitioner who is caring for that patient; and 3) for a single indication in a single course of treatment. The latter two points in particular appear to be very loosely interpreted by the clinics providing these treatments.

The concepts of 'minimal manipulation' and 'autologous use', while not officially part of the Order, but which in part appears to have been the intention of the Order, allowing for the

RESEARCH AUSTRALIA

intended exclusion of procedures such as skin, blood cells and bone grafts, also appears to be loosely interpreted.

Since the original exclusion of regulation under the Act was articulated, a wide range of therapies based on the use of autologous cells and tissues have emerged. This means that there is now a very strong case for much clearer definitions and more rigorous regulation under the Act of those human cells and tissues intended for autologous use.

MS Research Australia acknowledges that the rate of progress necessitated by a rigorous clinical trials process to define the risks and benefits of stem cell treatments may leave many individuals with MS and other chronic progressive disorders frustrated. We also understand and respect that all individuals, particularly those faced with a chronic, disabling disease, may have a different perception of, and attitude towards, risk. However it is essential that new treatments are introduced under a process that allows doctors and patients to make a fully informed assessment of the risks relative to the potential benefits.

This process will also ensure that advancements in the provision of new treatments to patients occurs in a safe manner that will also ultimately ensure equitable and affordable access to treatments by all individuals who may benefit from them.

Discussion paper questions

What are the public health risks of 'autologous stem cells' in your view?

Every medical intervention comes with a range of risks. Liposuction to retrieve adipose tissue, for example, while widely practised, has its own inherent risks, however, with the reinfusion of tissue or stem cells there are other additional risks. Attachment 2 of the TGA discussion paper provides a very clear review of the adverse events that have been identified to date. However, there are also potentially many risks that remain unknown and undefined, as the long-term follow-up studies have not been done.

The majority of medical interventions have been carefully studied through clinical trials and hospital-based studies to define and characterise the risks, as well as ensuring reproducible benefits of the intervention.

This allows both doctors and patients to make a carefully considered evaluation of the relative risks and benefits of the intervention and make a well-informed treatment decision based on that evaluation within the context of the patient's individual circumstances.

This is not the case with unproven 'autologous stem cell' therapies. Beyond the more obvious immediate risks associated with the removal and return of cells (such as infection), the long term risks have not yet been assessed. In addition, it is vital to understand the mechanisms behind any observed effects, including the survival (or otherwise) of re-introduced cells. Patients are therefore being exposed to unknown risks, for unknown benefit.

A further risk is that patients will put their faith in the long-promised 'era of stem cell therapies,' and the compelling advertising of the clinics offering these therapies, and forego proven treatments that are likely to provide real benefits for health and quality of life. The current lack of restrictions on direct-to-patient promotion of unproven stem cell therapies means that patients often access these therapies with little or no discussion with their treating doctors. This compromises the follow-up and care of these patients by health professionals and adverse events connected to stem cell treatments may go unrecognised as the doctor may be unaware that the patient has undergone such a treatment.

The financial outlay in obtaining unproven stem cell treatments is also considerable and has the potential to add to the reduced quality of life suffered by patients with a chronic condition.

What is the evidence for these risks?
As discussed in Attachment 2 of the TGA's discussion paper (Summary of TGA review of the safety of autologous adipose-derived mesenchymal stem cell therapies), "no significant safety issues pertaining to the therapeutic use of mesenchymal and/or adipose-derived stromal cells were identified based on published data..." However, the Summary also acknowledges that very few studies have been conducted of the use of adipose-derived tissue, and only *one* study was identified for the treatment of an autoimmune disease. Despite this absence of comprehensive risk assessment of these interventions, the Summary identifies a range of clearly defined risks and potentially serious adverse events identified within the published data.

The adverse events identified in the Summary are all of concern. However, it is particularly concerning that there is a "general lack of standardised cell characterisation and expansion protocols, combined with a paucity of knowledge with regard to biological context in which the cells operate *in vivo*..."

The risks of infusing a poorly defined preparation of cells back into the body are therefore very difficult to define, and this is compounded by the documented accumulation of abnormalities in cells that have been grown for any length of time in cell culture.

The lack of peer-reviewed studies also means that there is no evidence that these treatments do not in fact worsen the condition being treated. This is particularly concerning for autoimmune conditions such as MS, in which the potential for an adverse disturbance to the immune system that may worsen the disease course is very real. Additionally, any fever associated with even mild infections or infusion reactions has documented potential to exacerbate MS. The risks are also potentially compounded by a a range of co-morbidities that are common in people with chronic conditions.

What identified risks should have the highest priority for resolving?
It is imperative that the intervention should be shown not to cause a worsening of the disease and has a low risk of serious adverse events. However, for any new intervention the highest priority must be to define both the short-term and long-term risks as well as any

potential benefits so that an accurate, informed assessment can be made of the risk-benefit ratio of the intervention.

Are there public health benefits, such as patient access to new and novel treatments to consider?
Patient access to new and novel treatments is vital if advancements in treatments are to be made. However, this is readily achievable within the framework of clinical trials with the current system that includes registration of experimental interventions for use in clinical trials with the TGA. Clinical trials and well-designed long term observational studies will provide the necessary level of evidence for safety and efficacy of stem cell therapies to enable them to be safely and equitably provided to all patients who may benefit.

As discussed in more detail below, we strongly advocate for the regulation of autologous stem cells as set out in Option 5.

Options for the regulation of autologous stem cells

Option 1 – Continue to exclude autologous cells from regulation under the act
This option is inadequate. While it will continue to exclude tissues already outlined in Attachment 1 of the discussion document, and may bring some of the more complex tissue preparation processes under the regulation of the Act, there are no requirements for evidence of safety and efficacy, no requirement for reporting of adverse events, and no restrictions on advertising treatments of indeterminate safety or efficacy to the public, which are then marketed at very high cost to the individual. This option also would not stipulate the development of any standardised cell preparation or manufacture processes under the Good Manufacturing Practice and Good Clinical Practice codes. This could potentially expose patients to poorly prepared and poorly defined cell preparations, including cells that may have accumulated abnormalities through cell culture or cell expansion practices.

Option 2 – Exclude autologous stem cells from regulation under the Act in defined circumstances.
For option 2 to fully address the concerns articulated above, it will be necessary to have very rigorous and unambiguous definitions of homologous use and minimal manipulation, as well as the careful policing of practices to ensure that they comply with these definitions. There are likely to be many additional types of cells and processes that fall outside the boundaries of these definitions and into a grey area, and thus may escape the necessary oversight and regulation required to ensure safety.

As defined in the footnotes on pages 18 and 19 of the Discussion Paper, this would be likely to mean that the items listed in Attachment 1 would continue to fall within that exclusion.

More substantially manipulated cells such as adipose-derived cell preparations, for example, could come under the regulation of the Act under this option, which would be welcome. It would enable more complex cellular preparations to be regulated and prepared under good manufacturing practices.

RESEARCH AUSTRALIA

However, it is possible under this option that clinics may still be able to provide some unsafe and unproven forms of therapy. It may also lead to some clinics modifying their practice to deliver even less well-defined crude cellular preparations in their efforts to remain within the criteria for minimal manipulation.

It also, and most importantly, means that some unproven therapies will continue to be provided to patients with no requirement for reporting of adverse effects. This will potentially mean that unsafe therapies will never be identified.

The requirement under option 2 of no advertising to consumers would be welcome, however, the powerful use of patient advocates and 'word-of-mouth' will mean that many patients will still seek and find clinics that provide the unproven and unregulated forms of therapy.

Option 3: Regulate autologous stem cells under the Act, but exempt from registration and manufacturing requirements

Option 3 would appear to be a step in the right direction as it would bring all stem cells appropriately under the jurisdiction of the TGA. As per option 2 it may also be possible to exempt some very clearly defined types of practices involving minimally manipulated cells for homologous use, from the requirements for registration and manufacturing practices.

However, allowing for the exemption of some types of tissues from the manufacturing and registration process may still leave a significant loophole through which crude cell preparations are delivered to patients with no requirement for safe manufacturing practices or licensing of the clinic or practitioner.

Option 3 would bring all autologous stem cells under the requirement for reporting of adverse events, however, the provision of stem cell treatments by clinics that are not associated with the long term care of a patient, may mean that the necessary follow-up and reporting of adverse events that occur outside of the immediate period of treatment at the clinic are not detected.

Option 4: Regulate under the Act as Class 1 biologicals

Option 4 introduces a much more rigorous requirement for safety monitoring of all types of tissues as they will fall either under the category of class 1 biologicals or be fully regulated under the Act as class 2, 3, or 4 biologicals. It may provide an incentive to conduct clinical trials to provide the necessary evidence for the long-term safety of autologous stem cell treatments. It introduces an appropriate requirement for adverse event reporting.

With clear and rigorous definitions and policing of those definitions it is likely that most of the more concerning autologous 'stem cell' practices would then be brought under the regulation of the Act as class 2 biologicals, or higher.

For example, adipose-derived cell preparations which may be used for the treatment of autoimmune disorders such as MS, where the target for treatment is not adipose tissue but

the immune system and/or the nervous system, would not (and should not) be considered homologous use. The cell preparation processes would (and should) exceed the definition for minimal manipulation. This would then bring these cells under the regulation of the Act.

However, this may still leave the door open to many unproven cell 'therapies' that fall under the definition of Class 1 biologicals, but still do not have proven safety and the cell preparation process will not regulated under standardised good manufacturing practices.

Importantly, option 4 does not require any evidence for efficacy – again leaving vulnerable patients open to the expense and risks of a treatment that may not hold any potential benefits. As acknowledged in the TGA discussion paper, this level of TGA oversight, in the absence of requirements for evidence of efficacy, may have the 'inadvertent effect of providing an inappropriate level of confidence in the products'.

Option 5: Regulate under the Act as Class 2, Class 3 or Class 4 biologicals
Option 5 is the only option that introduces an adequate level of oversight in relation to the requirement for evidence of safety, efficacy and quality based on a dossier that will include clinical evidence from rigorously conducted clinical trials.

It will provide all necessary requirements for manufacturing standards and licensing, long term safety and adverse event reporting. It will prevent advertising to the public, but will not prevent patients from accessing treatments during the clinical trials process, or once approved, via referral following informed discussion with their treating physicians.

This is the only option that will ensure the safety and efficacy of these treatments must be established prior to use outside of the carefully controlled and safely monitored setting of clinical trials. This will ensure that patients and doctors have access to the necessary information regarding the risk versus benefit profiles of autologous stem cell treatments to enable fully informed treatment decisions.

It is also the only option that will facilitate the development of innovative new treatments in a safe manner, ultimately ensuring that safe and equitable access to potentially effective therapies can be accessed through the public health system so that all patients who need it can access it, rather than only those who can afford it.

Thank you once again for the opportunity to comment on this important discussion paper.

Dr Lisa Melton, Research Development Manager, MS Research Australia
With
Dr Matthew Miles, Chief Executive Officer
Dr Alana Shepherd, Research Development Coordinator