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Submission Re: ***Regulation of autologous stem cell therapies***

I am a Melbourne medical graduate who has worked in full-time specialist musculoskeletal pain medicine for 35 years. I am a Fellow of the Australasian Faculty of Musculoskeletal Medicine and have a Masters in Pain Medicine from Sydney University. I am a past-president of the Australasian Faculty of Musculoskeletal Medicine. I have edited medical textbooks on interventional pain management and written chapters in medical textbooks including chapters that describe the primary issues in my particular area of interest, which is spinal pain. I have also published numerous times in the medical research literature on subjects pertaining particularly to spinal pain.

As a researcher and medical clinician involved in the management of complex pain problems, I welcome the opportunity to provide input to the TGA's Consultation regarding the regulation of autologous stem cells. As diagnosis and management of spinal pain and especially complex back pain is my major medical interest my submission pertains specifically to this problem.

This submission will explain the impact that back problems on our society, not only in terms of disability, pain and suffering, but also in fiscal terms. We have a significant world wide problem and the current management is often ineffective, and costly. New medical and surgical innovations are proving more successful and cost-effective compared to older therapies, but these therapies are only for end-stage back problems, long after degenerative processes have begun and then destroyed all hope of natural healing. It is vitally important that the world discovers whether or not stem cells or any similar

treatment can truly and significantly reduce the prevalence, cost and disability of the severe long term outcome from many back injuries.

Background Information and Clinical Rationale for investigating Stem Cells for the prevention and/or Management of Low Back Pain

The problem

Low back pain (LBP) is a major health problem particularly in industrialized countries,[9] affecting approximately 60-80% of the adult population at some stage[8;13;34] and about 6% of people each day.[13] LBP affects up to 80% of the working population during their lifetime and is the second most common reason for physician visits,[16] and for work disability.[33] LBP is associated with substantial health care costs and absenteeism from work.[9;20;29]

In Australia, back problems are the most frequently seen musculoskeletal condition in general practice and the seventh most common reason for seeking care.[4] In Australia, a 2001 survey found the point prevalence of LBP to be 26%, the 12-month prevalence 68% and lifetime prevalence 79%.[34] Only about 50% of the adult population experience low-intensity pain and low disability from it and another 11% experience high intensity-pain but still low disability in 6-month period.[34] However, about 11% of the population experience high-disability LBP,[32;34] and it is to this group that most resources are directed.

LBP is a costly problem. In early 2000 the cost of headache, LBP, arthritis and other muscle and joint pain to USA employers was more than $60 billion per year (these costs may have been under-estimated, as lost productivity amongst workers affected by a co-workers diminished productivity was not taken into account).[26] The majority of these costs (77%) related to reduced performance rather than work absence (workers who experienced lost productive time from a pain condition lost a mean of 4.6 hours/week). Workers who reported arthritis or LBP had mean lost productive times of 5.2 hours/week. It was established that these pains were directly associated with a 13% loss in productive time. Headache was the most common (5.4%) pain condition resulting in lost productive time. It was followed by LBP (3.2%), arthritis pain (2.0%), and other musculoskeletal pain (2.0%).

Furthermore, the total health care expenditure only for LBP in the USA is even more alarming. When studied in 1998, total health care expenditures incurred by individuals with LBP in the USA reached

$90.7 billion and total incremental expenditures attributable to LBP among these persons were approximately $26.3 billion. On average, individuals with LBP incurred health care expenditures at 60% higher than people without LBP.[19] The lead researcher, Xuemei Luo, put these figures into the perspective of the USA economy by noting, “The total $90 billion spent in 1998 represented 1% of the U.S. Gross Domestic Product, and the $26 billion in direct back pain costs accounted for 2.5% of all health care expenditures for that year.”

The largest proportion of direct medical costs for LBP is spent on physical therapy (17%) and inpatient services (17%), followed by pharmacy (13%) and primary care (13%). However, indirect costs, especially resulting from lost work productivity, outweigh other costs substantially.[7]

The source of pain

The intervertebral disc (IVD) is the most common source of LBP, being the prime source in about 40% of complex chronic LBP presentations.[23] In many cases, the source of LBP is not found. Specifically, pathological degradation of the nucleus pulposus (NP) matrix with accompanying radial and/or concentric fissures in the annulus fibrosus (AF) is significantly associated with LBP.[23] Fissures can penetrate the annulus to varying degrees (graded I to V on an escalating scale). Internal disc disruption (IDD) is the diagnostic label given to a patient with LBP who is shown to have IVD degeneration on discography and in whom the patient's particular pain is reproduced in a specified manner when the disc is "provoked" in a procedure known as provocation discography.[5;31]

The etiology of IVD degeneration is also well established through biomechanical experiments demonstrating that the vertebral endplate is subject to fatigue failure, [1;11;17] causing de-aggregation of proteoglycans in the nucleus, a reduction in water content and consequent depressurisation of the NP, as well as delamination of the AF.[12]

Current minimally to more invasive therapies

In the management of disabling chronic LBP, once non-invasive options, such as pharmacological manipulation, exercise, physical therapy and pain management programs have been tried and failed, (and, by the way, these have zero or limited evidence anyway), invasive options can be considered. Unfortunately, interventions from the minimally invasive IDET and biacuplasty to the more invasive surgical methods, including spinal fusion with or without discectomy and NP prostheses and annuloplasty,[6;25;30] often yield uncompelling outcomes and suggest that other therapies should be considered, including the possibility of cell therapy strategies that can putatively regenerate the IVD, restore or improve its function, leading to clinical success.[18;27]

Surgical treatments have been assessed with pragmatic studies comparing one treatment versus another. For example, lumbar disc replacement with two devices (Kineflex-L Disc and CHARITE artificial disc) was found to be equally successful in about 90% of cases, but there was no comparison to other treatment and no sham treatment group.[10] However, one a more sobering level, a pragmatic study by a spinal surgery team in USA found that lumbar discectomy and fusion in patients with IDD was highly clinically successful in only 27% of patients and minimally clinically successful in only 43% of patients.[6]

Another treatment for severe back pain problems, and in particular LBP that persists after spinal surgery is spinal cord stimulation (SCS), a form of neuromodulation. Recent clinical trials have shown that SCS is likely to be superior to all other therapies for such difficult LBP patients.[2;28] Additionally, in the British Health System, such treatment has been found to be cost-effective in under two years from the treatment implementation despite the fact that such treatment is expensive.[3] Each treatment in Australia costs in the order of $45,000 just for the surgical treatment without the subsequent costs of further operation and rehabilitation. It becomes cost-effective because it substantially lowers pain, and the cost savings arise from lowered future use of the health system, lowered medication and return to work and normal function in a situation where other treatments typically achieve nothing despite being expensive.

It should also be noted that there are no therapies that have been designed and/or used for the prevention of painful disc degeneration after an injury has occurred. Treatments tend to be reserved for the end-stage presenting problem.

Preliminary information on stem cell therapies for LBP

Mesenchymal stem cells (MSCs) are a very attractive cell source for use in restoring the normal cellular constitution of the degenerated disc. MSCs are readily available (adipose, bone marrow or umbilical cord blood) and can be differentiated. Various studies suggest that these cells may be effective in the human IVD. [14;15]

To date, most research has focused on NP and 'off the shelf' allogeneic MSCs transplants, and although promising, donor derived allogeneic MSC therapy is not currently approved by the regulatory authorities for use in standard care. The alternative 'point-of-care' minimally manipulated, autologous MSC preparations performed under the supervision of the treating physician, represents an assumed safer approach by using the patient's own stem cells. A study of 10 patients with confirmed IDD injected with autologous MSCs, described rapid improvement in pain and disability at 3 months, followed by a modest improvement within 6 and 12 months after injection.[22] Whilst there appeared to be no improvement in disc height, the water content of the disc was significantly elevated at 12 months, suggesting a significant increase in NP cell content.

Animal model studies have documented the feasibility and effectiveness of NP cell transplantation, however, difficulties in obtaining sufficient NP cell numbers in a healthy state severely impacts on the validity of this therapeutic approach.[24] The number of NP cells responsive to growth factor stimulation

diminishes during degeneration, however, introducing cells capable of regenerating disc tissue may potentially reverse the disc degeneration, and reduce discogenic pain. As a corollary, studies on intra-discal growth factors alone have failed to pass placebo controlled testing, presumably because of the paucity of cells in a degenerating disc.

Allogeneic stem cells for the treatment of LBP have been studied on one occasion. This was a positive study. It was a 24 month Phase 2 study for chronic low back pain presented at the JP Morgan 33rd Annual Healthcare Conference held in San Francisco in January 2015. [21]

Ramifications for a randomized controlled study on autologous stem cell use in the management of LBP:

The efficacy of stem cells in the management of LBP can only be determined when numerous phase III studies are completed. I consider that these studies are required for autologous stem cells as it is likely that one method of extraction and application will be either better or worse than another. The technology for the safe extraction and delivery of these cells exists. The enormity of the LBP problem implies that we need to establish if there stem cell therapy is effective in the management of LBP, and furthermore, in reducing the rate of degeneration of the IVD once it commences so as to minimize or prevent chronic incapacitating LBP.

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