Ocular Stem Cell Therapy –

Joint RANZCO and Stem Cells Australia Position Statement

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Purpose and scope

This position statement is written in the context of current Australian and international guidelines and considers activities occurring outside the expected pathways to clinical translation. It has been written for stem cell (SC) experts, the broader medical community, and patient groups from an Australian perspective, with a view to being considered and potentially adapted internationally. The position statement is based on a comprehensive literature review, review of registered clinical trials (https://clinicaltrials.gov/), and input from experts in the field, including position statements from leading organisations.

Stem cells and their Therapeutic Utility in Ophthalmology

Ocular stem cells have emerged as a potential therapy for eye disease. Ocular surface failure due to loss of limbal stem cells, though uncommon (Bobba et al., 2017), is associated with significant disease morbidity (Geerling et al., 2002). Corneal-limbal stem cells cultivated as epithelial sheets have successfully been used to treat limbal stem cell deficiency with various carrier substrates, including human amniotic membrane, silicone hydrogel contact lenses and fibrin (Di Girolamo et al., 2009; Rama et al., 2010). Recently, a formulation of autologous corneal-limbal progenitor cells cultivated on fibrin matrices has become available as a licensed therapy in Europe (Abou-El-Eneim M et al., 2016). The potential role of corneal-limbal mesenchymal stem cells in ocular stem cell transplantation is unclear, but it is an ongoing area of investigation within Australia and overseas (Harkin et al., 2015). Stem cell therapies are also being considered as potential treatment for common causes of blindness, such as age-related macular degeneration (AMD) and inherited retinal diseases (Baker et al., 2009). Although most studies on retinal stem cell transplantation remain in pre-clinical stages, Phase I/II clinical trials have demonstrated short-term safety in patients with AMD (Schwartz et al., 2015; Song et al., 2015; Mandai et al., 2017) and are underway in patients with IRDs.

Despite the potential benefits of ocular regenerative techniques, stem cell therapy is not without significant risks and ethical implications. Safety considerations include the risks of systemic immune suppression and transplant rejection with allogeneic stem cell sources (Trickett et al., 2011; Trounson et al., 2015). Additionally, our current understanding of the epigenetic state and memory of reprogrammed cells is limited. Patient-specific genetic polymorphisms for certain ocular diseases may be expressed by autologous induced pluripotent stem cells or adult stem cells and theoretically be associated with an increased recurrence risk (Wiley et al., 2015). The exact mechanism by which ocular stem cells are transplanted is poorly understood, with debate continuing over whether the transplanted cells reactivate quiescent cells or provide a new source of cells. Furthermore, considerations such as obtaining donor consent (McCaughey et al., 2016) and screening for infectious diseases need to be incorporated into study protocols to ensure compliance with Good Manufacturing Practice (GMP) standards. Long-term follow-up is needed to determine the potential risks of ocular stem cell transplantation, such as oncogenic mutations and unwanted cellular proliferation. Ultimately, larger scale studies with longer follow-up duration are required to validate the safety and efficacy of ocular stem cell transplantation in patients before the transition is made from pre-clinical and clinical trials to clinical practice.

Regulatory oversight in Australia

Within Australia, the Australian Medical Association Code of Ethics details the need for adequately designed ethically approved research, informed patient consent and

consideration of patient wellbeing. This is in keeping with the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) Code of Conduct, which outlines expected professional behavioural standards for ophthalmologists. In Australia, compliance with Therapeutic Goods Administration (TGA) standards for the manufacture and delivery of cell-based therapies is considered best practice. However, in cases where they are obtained from and returned to the same patient under the care of a medical practitioner in a single treatment, cell-based therapies are exempted from GMP standards (Trickett and Wall, 2011; TGA, 2017). Conventional hematopoietic stem cell transplants are highly regulated by agencies other than the TGA. It had been envisaged that the manufacturing and clinical use of novel stem cell-based interventions would fall under the TGA's remit with clinical trials also having to abide by the National Health and Medical Research Council (NHMRC) guidelines, including those outlined in the *National Statement of Ethical Conduct in Human Research 2007* (NHMRC, 2015). This includes the requirement to register any clinical trial involving a non-TGA approved therapy with the Clinical Trials Notification Scheme and typically mandates that the therapy proceed through the four phases of clinical trials as per NHMRC guidelines.

When the Biologicals Framework was introduced, all autologous-based cell and tissue therapies were broadly excluded from having to comply. As a result of this exclusion, there was an increase in the number of clinics offering autologous interventions for a myriad of conditions ranging from anti-aging, infertility and erectile dysfunction to osteoarthritis, Parkinson's disease and multiple sclerosis (Munsie and Pera, 2014). This largely unregulated industry has continued to grow, from two clinics in 2011 to over 70 charging patients for non-evidence-based interventions (Munsie et al., 2017). While the treatment of vision loss is not common, there is at least one clinic offering treatment.

Notably, there is currently no requirement for these stem cell clinics to use accredited laboratories, standardise protocols, characterise the material injected into the patients, report adverse events or restrict their services to evidence-based practices. In response to concerns about these practices, the TGA recently announced that they will introduce changes in 2018 to provide greater regulatory oversight of products derived from autologous cells commensurate with the safety risks that they pose to patients (TGA, 2017). The TGA proposed regulation of all autologous cells and tissue products offered outside an accredited hospital setting, with possible exemptions depending on the degree of manipulation and whether the intended use is homologous or not. Direct to consumer advertising of autologous products will be banned, however "services" will still be permitted. Health practitioners, now proposed to include dentists as well as medical practitioners, will be exempt provided the manufacturing and administration is contracted within an accredited hospital. Access to unapproved treatment options will still be available via the Special Access Scheme and through clinical trials.

RANZCO Position Statement

Based on the literature and ethical considerations, RANZCO has developed a position that supports advancements in knowledge, which are imperative to improving patient care. It endeavours to minimise patient harm in this venture, promoting patient autonomy and safety as key priorities. RANZCO supports the use of stem cells for ocular disease in accordance with the RANZCO Code of Conduct, namely:

1. as part of a clinical trial registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR) or appropriate international clinical trial registry, as well as complying with ethics review and approval from a registered human research ethics committee;

2. RANZCO strongly cautions practitioners regarding risks for patient safety and mandates that formal ethics approval is obtained in all cases, including compassionate use;
3. following pre-clinical/animal models that have gained approval from a registered Animal Research Ethics Committee; and
4. with peer review in the process of establishing clinical trials for a stem cell intervention.

Moreover, based on an extensive review of the literature, TGA guidelines and expert opinions in the field, RANZCO is of the opinion that:

1. The literature to date suggests that the use of corneal-limbal epithelial stem cells for ocular surface transplantation is a viable therapy based on Phase I/II clinical trials, and that the development of more robust clinical trials with long-term follow-up is reasonable.
2. Based upon the literature, further pre-clinical and clinical trials of human induced pluripotent stem cells (iPSCs) and human embryonic stem cells (hESCs), mesenchymal stem cells, photoreceptor progenitor and all other potential types of stem cell sources should be conducted. Investigation of iPSC/hESC-retinal pigment epithelium for the treatment of AMD should be given particular priority in light of recent clinical evidence and the growing number of Australians affected by this condition.
3. Knowledge dissemination of high quality evidence is imperative to improving patient care.
4. RANZCO members must inform all participants receiving ocular stem cell therapy including as part of a registered ethics-approved clinical trial and those undergoing compassionate interventions that they are undergoing stem cell intervention which is novel and/or experimental and for which the long-term effects are yet to be established. Any conflicts of interest should be declared.
5. The RANZCO position is that patient autonomy and safety are key priorities, ensuring that all therapies and treatments endeavour to minimise patient harm.
6. Registries are an additional tool to collect treatment and patient outcomes data and should have a role in post-market surveillance of stem cell therapies.
7. Regulatory reform of current stem cell practices is welcome and implementation of such reforms should be supported.
8. All instances of use of stem cell therapy are subject to audit by the investigators, comparable to introduction of new surgical procedures.

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