Simerdip Kaur takes a look at the latest ophthalmology-related news stories and asks which are based on facts and which are 'fake news'.

Headline: *Patients blinded by stem cells! How safe are they really?*

Ever since the successful results following human embryonic stem cell (hESC)-retinal pigment epithelium (RPE) implant in two exudative age-related macular degeneration (AMD) patients by Professor Da Cruz and his team at Moorfields Eye Hospital, more and more patients in medical retina clinics have been enquiring and even requesting this treatment. But what do patients understand about stem cells in the first place? How do we counsel our patients about stem cell therapy?

Broadly speaking, stem cells are cells that have the ability to differentiate into other specialised cell types. There are two main types, embryonic and adult or tissue-specific stem cells [1]. The former is obtained from a human embryo in its blastocyst phase usually following in-vitro fertilisation (IVF), whilst the latter is derived from virtually any tissue in the body such as bone marrow, blood, skin, fat and skeletal muscles. The advantage of embryonic stem cells are its pluripotent ability allowing it to differentiate into any type of cell in the body arising from the three germ layers: endoderm, mesoderm and ectoderm, whilst adult stem cells are multipotent, i.e. they are able to differentiate into limited and discrete cell types as dictated by previous differentiation [2].

In 2015, two women with dry and one with exudative AMD were blinded following intravitreal injections of their own adipose-tissue derived stem cells (ADSCs) following a liposuction procedure in a Florida clinic [3]. The use of ADSCs which are classified as multipotent is on the rise both in the UK and the US, particularly in regenerative medicine, due to the ease in which they can be harvested and their anti-inflammatory, immunomodulatory properties. They are being used to treat conditions such as multiple sclerosis, for soft and skeletal tissue repair and myocardium regeneration, to name a few, with encouraging outcomes [4]. Sadly, the Florida clinic patients developed retinal detachments with proliferative vitreoretinopathy, likely due to impurities in the stem cell preparation [3]. These patients were under the impression that the treatment they received was within the context of a clinical trial as it was listed on ClinicalTrials.gov that is overseen by the National Institutes of Health (NIH) and also paid $5000 each. ClinicalTrials.gov is simply a study repository and the NIH does not endorse any of the studies listed on its website beyond ensuring basic quality control. Kuriyan (2018) initially reported these cases and in his latest study uncovered that there still remains a huge supply of 'cell therapy' clinics in the USA offering these experimental treatments for AMD despite not having Food and Drug Administration (FDA) approval [3,5].

This is in stark contrast to the promising phase 1, open-label, safety and feasibility study involving the transplant of differentiated hESC-RPE on two patients with severe exudative AMD conducted by Prof Da Cruz and his team [6]. These cells sit on a coated synthetic membrane, thus conferring the appearance of a patch that can be easily handled by a special purpose built microsurgical device to deliver it to the subretinal space under the fovea. These patients received oral steroids perioperatively and were subsequently immunosuppressed with intraocular steroid implants long-term to ensure long-term hESC-RPE survival. There were three adverse events noted, including suture exposure of the steroid implant, worsening of diabetes and a retinal detachment, all of which were managed appropriately. At 12 months, there was no evidence of neoplastic transformation in either patient. Both patients had improvement in their vision, reading speed and contrast sensitivity. Unlike the cell therapy clinics in the US, pre-clinical studies were conducted on pigs and mice eyes, which confirmed surgical practicality, as well as the absence of local or systemic distribution of hESC-RPE cells confirming its safety profile [6].

Unsurprisingly, stem cell research has not treaded an entirely rosy path especially with regard to the ethical debates surrounding the use of hESC.

In 2012, scientists John Hurdon and Shinya Yamanaka won a Nobel prize in medicine for their discovery of induced pluripotent stem cells (iPSC) that could potentially replace the need for hESC in the future [7]. iPSCsare artificially derived from mature adult somatic cells and reprogrammed using embryonic transcription factors to allow for pluripotency [8]. There have been several studies on the use of iPSC for AMD, most notably by Takahashi et al. (2017), whereby they implanted the first autologous iPSC-derived retinal graft sheet in a patient with exudative AMD [9]. The patient's own skin cells were differentiated into RPE cells and transplanted under her fovea. A year later, the patient's vision remained the same with no sign of rejection and 25 months later no adverse effects were noted. Takahashi and her colleagues are currently undertaking a further trial using allogeneic iPSC in a suspension form and have transplanted these cells into one patient thus far [10]. They plan to recruit and perform this procedure in at least five patients over the course of two years to assess its safety and feasibility driven by the reduced cost and time taken to cultivate these cells for transplantation.

Stem cell therapy in ophthalmology is inching closer to becoming scientific reality. However, there is still a long way to go, and in the interim, patient education on their disease and current approved treatments is of the utmost importance. Patients need to be wary of stem cell clinics offering miracle cures for conditions such as AMD and advised to look out for regulatory approval of the proposed treatment. They should also ensure that validated and reviewed evidence of pre-clinical studies of the proposed treatment exists. Patients should not have to pay for the treatment if it is part of a trial and, most importantly, both eyes should not be treated at the same time.

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