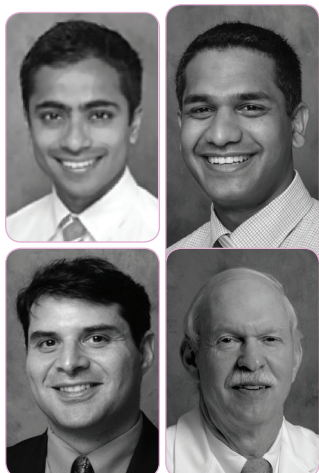


BUYER BEWARE: IGNORANCE ≠ BLISS

Unregulated stem cell clinics pose real risks to patients with AMD.

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Research in the field of stem cell therapy blossomed in the first decade of this century as a result of a major technological breakthrough in which somatic mouse cells were reverse-engineered into inducible pluripotent stem cells that could then be “shaped” into specific cell types.¹ There has since been a wide-ranging attempt by members of the scientific community to find clinical applications for stem cell technology in all fields of medicine. Medical models

have shown promise in the development of stem cell cardiac myocytes,^{2,3} neuronal tissue,⁴ and liver hepatocytes.^{5,6}

In retina, the seminal work of Lund et al introduced the concept of genetically engineered human retinal pigment epithelium (RPE) transplantation into the subretinal space in mice.⁷ Using a mouse model that simulated the retinal architecture of patients with age-related macular degeneration (AMD), Lund and colleagues successfully injected RPE cells into areas devoid of this critical layer and showed incorporation of the stem cells and potential reconstitution of the retinal architecture.

FURTHER RESEARCH

Nearly a decade after that work was published, Schwartz et al conducted a small multicenter phase 1/2 open-label human case series utilizing human embryonic stem cell-derived RPE (hESC-RPE) in patients with end-stage nonexudative AMD and Stargardt macular dystrophy.⁸ This trial showed that hESC-RPE cells could be transplanted into patients with accuracy and without the feared complication of tumor development. Patients also showed a slight improvement on objective parameters: Of the 18 eyes of 18 patients included in the study, BCVA improved in 10, improved or remained the same in seven, and decreased by 10 letters or more in one. Untreated fellow eyes did not show similar improvements in visual acuity. Results of visual functional questionnaires indicated that most patients

experienced subjective improvement. In a finding that will be important for monitoring results, RPE transplants could be easily tracked using traditional optical coherence tomography imaging. Adverse events that were associated with transplantation included one case of endophthalmitis and development of cataracts in four patients.

Since the Schwartz et al paper, a number of studies sponsored by industry or academia have examined the application of stem cells in the treatment of a variety of retinal disorders by novel delivery systems. For example, Regenerative Patch Technology is attempting to deliver cells on a synthetic pseudomembrane to mimic the retina's native Bruch membrane,⁹ and NeuroTech has been working on an encapsulated cell therapy in which stem cells are engineered to secrete anti-VEGF compounds and are placed as a depot subretinally, possibly mitigating the need for repeated injections.¹⁰ Other groups are attempting to engineer and transplant the photoreceptors themselves. A total of 13 trials involving the intravitreal injection of various stem-cell populations are registered at ClinicalTrials.gov.

WHEN THINGS GO WRONG

Although advances in stem cell therapy have shown promise, there are notable caveats. National attention



AT A GLANCE

- A number of ongoing studies are looking at the application of stem cells in the treatment of retinal disorders.
- Although the advances made in stem cell therapy have shown promise for the treatment of nonexudative AMD, there are notable caveats.
- It is incumbent upon the scientific and ophthalmologic communities to provide the most accurate information to patients regarding available and investigational stem cell treatments.

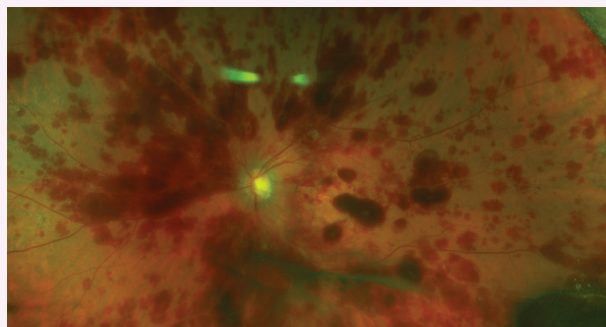


Figure. Diffuse preretinal and intraretinal hemorrhage is seen in this fundus photo of the left eye of a patient 13 days after intravitreal “stem cell” injection. Collections of cells can be seen in the vitreous cavity below the optic nerve and in the lower right corner. This retina detached 3 weeks later.

has been drawn to a small case series published in the *New England Journal of Medicine* highlighting eyes that were injected with same day, bilateral, autologous adipose tissue–derived “stem cells” for AMD.¹¹ The results of this for-cash procedure were devastating, with patients developing severe retinal detachments and/or hemorrhaging after injection, resulting in visual loss with acuities ranging from 20/200 to no light perception (Figure). These outcomes are dramatically worse than the typical 1-year outcomes of vitamin-supplement–treated AMD.¹²

A number of factors led to this unfortunate situation. Patients remain frustrated with current treatment options for AMD and are eager to find more promising therapies. Stem cell therapy clinics in the United States number in the hundreds and are operating outside the regulatory oversight of the US Food and Drug Administration (FDA) or any other regulatory body, most notably without demonstration of safety or efficacy in any scientifically rigorous way. These “stem cell” clinics have been financially successful, particularly in the treatment of joint disorders (although, again, rigorous scientific proof of efficacy is lacking) and are now naively branching out into other therapeutic areas, including ocular disease. The personnel employed by these clinics often lack sufficient training in ophthalmic therapeutics or research to safely perform procedures or to design studies in ethically or scientifically acceptable ways.

These events cast an important light on the way stem cell therapies and research should be regulated and conducted in the future, both in the field of retina and beyond. Although numerous stem cell therapies for medical disorders are being investigated at research institutions with appropriate regulatory oversight, some stem cell clinics are treating patients with atypical research protocols and without appropriate oversight and FDA safety monitoring. These programs often require the patient to pay out of pocket at nonacademic centers, and procedures are performed without the filing of an investigational new drug application with the FDA, which would require extensive safety data and monitoring protocols.

SAVE SIGHT: INFORM YOUR PATIENTS

Although stem cell transplantation appears to show promise in the treatment of nonexudative AMD, we emphasize that the benefits demonstrated to date have been modest and are not without possible complications, even in carefully regulated clinical trials. Attention must also be drawn to ocular stem cell studies that have poor regulatory oversight. It is incumbent upon the scientific and ophthalmologic communities to provide the most accurate information to our patients regarding available and investigational stem cell treatments. ■

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