EDITORIAL

The Growing "Stem Cell Clinic" Problem

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THE RESULTS OF A STUDY BY SCHWARTZ AND ASSOCIates[1] using subretinal transplantation of human embryonic stem cell–derived retinal pigment epithelium cells in patients with Stargardt macular dystrophy and atrophic age-related macular degeneration (AMD) has bolstered hope for using stem cell therapies for retinal diseases. This study reported that transplantation was safe and results in improvement in vision and vision-related quality of life, with a median of 22 months follow-up.[1] The scientific and clinical communities, along with patients with retinal diseases, are eagerly looking forward to the results of the other 35 studies listed on Clinicaltrials.gov that focus on the therapeutic stem cell use for retinal disorders.

Whereas scientifically rigorous studies of the therapeutic use of stem cells will provide us with the data and information necessary to move forward with these treatments, so-called "stem cell clinics," under the guise of research or established treatments, threaten to undermine both scientific progress and public trust in stem cell research. Stem cell clinics in the United States (U.S.) and abroad offer "stem cell treatments" for numerous disorders in ophthalmology and other specialties. Because these therapies are not approved by the Food and Drug Administration (FDA) and are not covered by insurance, the patients are left to pay for these interventions out of pocket, in some cases up to $50 000 for the procedures.[2,3] The lack of rigorous evidence of efficacy for these interventions is overcome by glossy websites and unsubstantiated testimonials.[4] Listing studies on Clinicaltrials.gov by these stem cell clinics may also give patients a false sense of security owing to a misunderstanding about the significance of having a trial listed on the website. Although the site is meant to be an inclusive repository of clinical studies, it does not effectively distinguish legitimate research from poorly thought-out or even concocted studies that are used as marketing tools for clinics marketing unproven therapies.

The issue of stem cell clinics abroad have received attention owing to complications, including development of a glioproliferative lesion of the spinal cord after intrathecal stem cell infusions in China, Argentina, and Mexico.[5] However, the U.S. was found to have the largest number of stem cell clinic websites, with 187 unique websites offering interventions at 215 clinics, in a 2016 study.[6] Another 2016 study found a total of 351 businesses performing direct-to-consumer marketing of stem cell treatments at 570 clinics.[7]

A recently published case series involved 3 patients suffering blinding complications from bilateral intravitreal injections of adipose-derived stem cell injections for AMD in the U.S.[8] The stem cell clinic had an active "study" on intravitreal stem cell injection for dry AMD listed on Clincialtrials.gov, but the 3 patients were not enrolled in the study and did not meet the listed study eligibility criteria. The preinjection vision in the better-seeing eye for these patients ranged from 20/30 to 20/50. The patients experienced retinal and vitreous hemorrhage, retinal detachments with proliferative vitreoretinopathy, and zonular weakness after the injections. One year postinjection, vision in the better-seeing eye ranged from 20/200 to no light perception.

The American Academy of Ophthalmology issued a clinical statement in 2016 emphasizing that there are no FDA-approved stem cell therapies for ocular diseases and that the risks of treatments at these stem cell clinics are not known. Stem cell clinics that use autologous stem cells contend that the cells are minimally manipulated cells and applied for homologous use, so they do not fall under strict regulatory oversight.[3,9] However, the FDA issued a draft guidance statement in December 2014 explaining the definition of "minimally manipulated" and another draft guidance in October 2015 to further delineate homologous use, in order to clarify that the use of autologous stem cells does fall under the regulatory oversight of the FDA.[10,11]

One of the common features of the 3 cases reported, and other cases of complications after stem cell clinic treatments, is that the patients paid out of pocket for their treatments.[5,8,12] An alarming feature in this report was the use of bilateral intravitreal injection of an unproven therapy without a track record of safety and success. Although bilateral intravitreal injections of commonly used medications are performed by retina specialists, experimental therapies are not given in both eyes in well-regulated clinical trials. Patients need to be informed

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that out-of-pocket expenses and bilateral experimental treatments are not typical practices in standard clinical trials, and patients should be skeptical of any clinic with such practices.

The practices of these stem cell clinics warrant further scrutiny by regulatory agencies to help protect patients. It is difficult to advise patients about the risk and benefit of treatments without efficacy and safety data, almost always obtained in lengthy and costly clinical trials. It is imperative to distinguish the opportunistic practices of these clinics from the positive work being done toward the clinical use of stem cells by rigorous scientific clinical trials. The promise of stem cell therapy for retina diseases is bright and should not be clouded by the practices of these stem cell clinics—rather, we need to work to better educate patients about the risks of stem cell clinics and work with regulatory bodies to effectively stop the predatory practices of these stem cell clinics.

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REFERENCES

1. Schwartz SD, Regillo CD, Lam BL, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. *Lancet* 2015;385(9967):509–516.
2. Connolly R, O'Brien T, Flaherty G. Stem cell tourism - a web-based analysis of clinical services available to international travellers. *Travel Med Infect Dis Phila* 2014;12(6):695–701.
3. Taylor-Weiner H, Graff Zivin J. Medicine's Wild West — unlicensed stem-cell clinics in the United States. *N Engl J Med* 2015;373(11):985–987.
4. Lau D, Ogbogu U, Taylor B, Stafinski T, Menon D, Caulfield T. Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine. *Cell Stem Cell* 2008;3(6):591–594.
5. Berkowitz AL, Miller MB, Mir SA, et al. Glioproliferative lesion of the spinal cord as a complication of "stem-cell tourism". *N Engl J Med* 2016;375(2):196–198.
6. Berger I, Ahmad A, Bansal A, Kapoor T, Sipp D, Rasko JEJ. Global distribution of businesses marketing stem cell-based interventions. *Cell Stem Cell* 2016;19(2):158–162.
7. Turner L, Knoepfler P. Selling stem cells in the USA: assessing the direct-to-consumer industry. *Cell Stem Cell* 2016;19(2):154–157.
8. Kuriyan AE, Albini TA, Townsend JH, et al. Vision loss after intravitreal injection of autologous "stem cells" for AMD. *N Engl J Med* 2017;376(11):1047–1053.
9. Parke DW, Lum F, McLeod SD. Stem cell treatment: think twice if they ask for payment. *Ophthalmology* 2016;123(10):S62–S63.
10. Minimal manipulation of human cells, tissues and cellular and tissue-based products: draft guidance for industry and Food and Drug Administration staff. Silver Spring, MD: Food and Drug Administration; December 2014. Available at www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/Guidances/cellularandgenetherapy/ucm427692.htm, Accessed March 16, 2017.
11. Homologous use of human cells, tissues, and cellular and tissue-based products. Draft guidance for industry and Food and Drug Administration staff. Silver Spring, MD: Food and Drug Administration; October 2015. Available at www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/Guidances/Tissue/UCM469751.pdf, Accessed March 16, 2017.
12. Leung EH, Flynn HW, Albini TA, Medina CA. Retinal detachment after subretinal stem cell transplantation. *Ophthalmic Surg Lasers Imaging Retina* 2016;47(6):600–601.