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Research Article

Stem Cell Ophthalmology Treatment Study (SCOTS): Autologous Bone-Marrow Derived Stem Cells in the Treatment of Hereditary Macular Degeneration

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Abstract

Purpose: We report a case of hereditary macular degeneration showing drusen and macular atrophy, clinically considered consistent with Malattia Leventinese, which obtained a significant improvement in vision following treatment with autologous Bone Marrow Derived Stem Cells (BMSC) in the Stem Cell Ophthalmology Treatment Study (SCOTS) National Clinical Trial Number 01920867.

Methods: A 53 year old male presented with a history of hereditary macular degeneration showing geographic atrophy and drusen, thought consistent with Malattia Leventinese. Screening examination showed best-corrected vision of 20/400 in the right eye (OD) and 20/2000 in the left eye (OS). Patient met inclusion criteria of SCOTS and underwent Arm 2 OD consisting of BMSC provided retrobulbar, subtenons and intravitreal; Arm 3 OS consisting of vitrectomy followed by BMSC provided subretinal and subtenons; followed by BMSC intravenous. Procedures were performed without complications.

Results: Pre-treatment and post-treatment comprehensive eye examinations were performed by the patient's eye physicians at a major university unassociated with the SCOTS study. Following treatment in SCOTS there was prompt improvement in vision which persisted. The patient's corrected Snellen visual acuity improved from 20/400 right eye (OD) and 20/2000 left eye (OS) pre-treatment to a final 20/25 OD and 20/40+2 OS at 14 months post-treatment.

Conclusions: A case of hereditary macular degeneration, thought clinically consistent with Malattia Leventinese (ML), was treated in the SCOTS clinical trial with autologous BMSC. The major improvement in vision that resulted suggests maculopathies showing drusen and atrophy may respond in a strong fashion to treatment with BMSC.

Keywords: *Malattia Leventinese; Macular Degeneration; Retinal Dystrophy; Familial Dominant Drusen; Bone Marrow Derived Stem Cells; SCOTS*

Introduction

Hereditary maculopathies are typically diagnosed clinically and differentiated from the common Age Related Macular Degeneration (AMD) by earlier onset, family history and specific retinal appearance. Although genetic testing can identify known associated genetic mutations, not all clinical conditions correlate perfectly with genetic findings. Malattia Leventinese (ML), also known as familial dominant drusen, autosomal dominant drusen or Doyne honeycomb retinal dystrophy [1-3], is a hereditary macular degeneration associated with a genetic defect that encodes for the protein fibulin 3 or Epidermal Growth Factor containing fibulin like extracellular matrix protein 1 (EFEMP1). It is inherited in an autosomal dominant pattern [4-6]. Yellow-white drusen are seen either peripapillary or in a radiating pattern posteriorly. Fluorescein angiography demonstrates the presence of extensive drusen and atrophy. Ophthalmoscopic findings may be

seen in the early second decade of life, though patients may remain asymptomatic into the fourth decade of life. Over time, the confluence of drusen and continued retinal pigment epithelial atrophy leads to visual loss. A choroidal neovascular membrane may occur, leading to further loss of vision [7]. This condition may be confused with Age-related macular degeneration, Stargardts disease, Sorsby macular dystrophy, the pattern dystrophies, Zermatt macular dystrophy, and late stage Best Disease. There are no established treatments available for this condition.

We have previously reported the treatment of a 77 year-old male with long standing visual loss from serpiginous choroidopathy treated with bone marrow derived stem cells (BMSC) within the Stem Cell Ophthalmology Treatment Study (SCOTS) [8]. Eight months after treatment with BMSC, the patient's best corrected Snellen acuity improved from 20/80- to 20/60+1 in the right eye and from 20/50- to 20/20-3 in the left eye. With the improvement in visual acuity, a corresponding increase in the macular volume as determined by optical coherence tomography was also noted.

Materials and Methods

SCOTS, the Stem Cell Ophthalmology Treatment Study, is the largest ophthalmology stem cell study registered with the National Institutes of Health- NCT Number 01920867. This has now been continued as the Stem Cell Ophthalmology Treatment Study II or SCOTS 2, NCT 03011541. SCOTS is a non-randomized, open label study evaluating the effectiveness of Bone Marrow Derived Stem Cells including Mesenchymal Stem Cells (BMSC) in the treatment of retinal and optic nerve disease. All patients enrolled in the study after eligibility criteria are met receive BMSC treatment. Both eyes are treated if both are eligible as the study is only concerned with ocular disease that is not known to spontaneously improve or is progressive. Eyes do not receive sham treatment or placebo. Bone marrow aspirated from the posterior iliac crest is separated to provide Bone Marrow Derived Stem Cells (BMSC) within the stem cell concentrate. Inclusion criteria for SCOTS provide that patients:

- Patients will have changes to the retina or optic nerve believed not likely to improve spontaneously OR have changes to the retina or optic nerve that are progressing.
- Best corrected visual acuity will be 20/40 or less in at least one eye AND/OR loss of visual field in at least one eye.
- Any prior surgical treatment for eye disease will have occurred at least 3 months prior to treatment.
- If receiving medical therapy for retinal or optic nerve disease patients should be thought visually stable on that intervention.
- Patients should be thought capable of improvement from treatment in the study and be unlikely to worsen as a result of treatment.
- Patients must be 18 years of age or older.
- Patients must be medically cleared by their primary care physician for anesthesia and to participate in the study.

Exclusion criteria include:

- Being unable to undergo ophthalmic evaluation.
- Being unable or unwilling to provide subsequent eye exams.
- Being unable to provide informed consent.
- Being at major risk to their overall health or to the eyes and vision by participating in the study.

There are three arms of SCOTS with the type of treatment chosen based on the degree of visual loss, etiology of visual loss, associated risk factors for the treatment arms and the patient's medical risk status. Bilateral treatment is provided assuming both eyes meet eligibility requirements. As these are autologous stem cells, no immunosuppression is required. An FDA cleared class 2 medical device is used to separate the bone marrow aspirate into a stem cell concentrate. This concentrate has averaged 1.2 billion Total Nucleated Cells

including mesenchymal stem cells in approximately 14 -15 cc of concentrate. Retrobulbar injection consists of 3 ml^3 of concentrate; subtenons injection of 1 ml^3; intravitreal injection of 0.05 ml^3; subretinal injection of approximately 0.1 ml^3 and intra-optic nerve injection of approximately 0.1 ml^3. The intravenous injection is provided from the remainder of the concentrate.

Arm 1 consists of stem cell concentrate injected retrobulbar and subtenons followed by intravenous infusion. Patients with ophthalmic conditions which preclude safe or effective utilization of intravitreal injection of concentrate, such as the presence of silicone oil, may be offered Arm 1 if meeting inclusion criteria. Arm 2 consists of the administration of retrobulbar, subtenon and intravitreal concentrate followed by intravenous infusion. Patients meeting inclusion criteria with visual acuity between 20/40 and 20/200 in one or both eyes and/or visual field loss may be offered Arm 2. Arm 3 is reserved for retinal and optic nerve patients with severe visual loss meaning visual acuity of 20/200 or worse in at least one eye. Typically, patients admitted to Arm 3 have much poorer vision. Arm 3 consists of the better seeing eye receiving the same treatment as Arm 1 or, Arm 2, and the eye with more extensive visual acuity loss receiving a core pars plana vitrectomy with injection of subretinal or intra-optic nerve concentrate followed by the infusion of intravenous stem cells. Monocular patients are not eligible for Arm 3. Follow up is required at 1, 3, 6 and 12 months post treatment with reporting of the eye exam results to the Principal Investigator and Study Director.

Unlike pharmaceutical studies in which a specific condition is treated, SCOTS focuses on the endpoint of visual loss, not the instigating cause. This allows the treatment of various retinal and optic nerve diseases, many of which are not presently the subject of clinical treatment studies, and include visual loss resulting from more than one disease.

The SCOTS procedure is patient funded and typically performed under general anesthesia. Treatment is provided in a fully licensed ambulatory surgical center in Coconut Creek, Florida.

Results

Case Presentation

This 53 year-old male reported a 13 year history of visual loss secondary to Malattia Leventinese (Familial Dominant Drusen) (Figure 1 and 2). His mother was also diagnosed with this condition. The patient's medical history was positive for treated hypertension and he was status post gastric bypass surgery for obesity. On May 20, 2014, the retinal ophthalmic exam at Vanderbilt Eye Institute, a major university in the southeastern United States, showed best-corrected vision of 20/400 in the right eye (OD) and 2/200 or 20/2000 in the left eye (OS). Amsler grid testing revealed bilateral central scotomas. Biomicroscopic examination was significant for mild bilateral cataracts. By dilated fundus examination radiating drusen and significant posterior pole atrophy was seen bilaterally. The central thickness as measured by ocular coherence tomography was 167 microns OD and 211 microns OS.

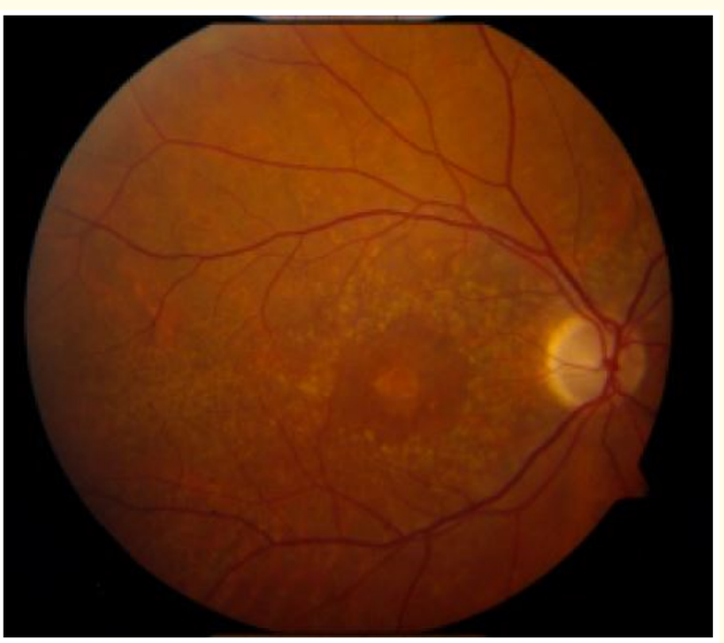

Figure 1: *Preoperative fundus photograph OD.*

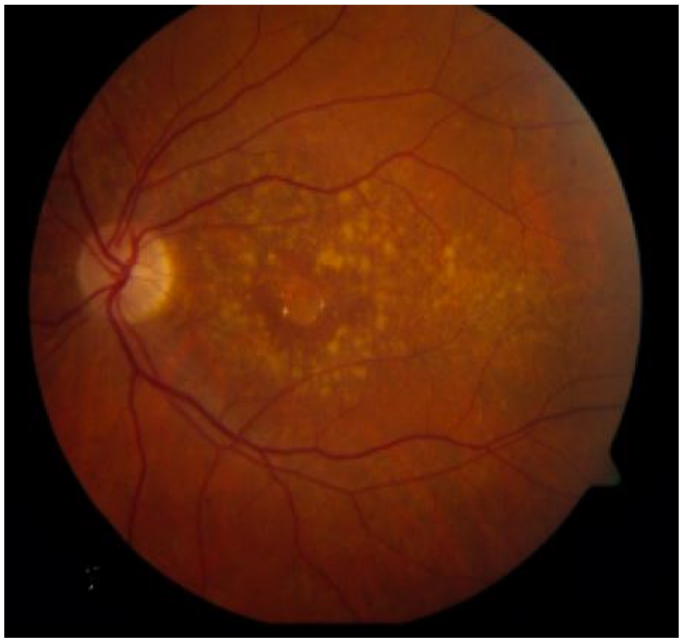

Figure 2: *Preoperative fundus photograph OS.*

In August 2015, following detailed informed consent, the patient was assigned to SCOTS Arm 2 OD and Arm 3 OS. BMSC were administered retrobulbar, subtenons and intravitreal OD. Following vitrectomy, BMSC were administered subretinal, and subtenons OS followed by intravenous BMSC. The procedure was performed without complications.

On the first postoperative day, the patient reported an improvement in visual acuity OD. Testing revealed a visual acuity of 20/70, ETDRS 20/80+1 OD. The visual acuity was unchanged OS. Two days later (3 days postoperatively) the visual acuity OD further improved to 20/60, ETDRS 20/50 and there was improvement OS to 20/60+2, ETDRS 20/50+2.

Within 1 month postoperatively the patient successfully passed his driver's test and obtained a driver's license. Subsequent Vanderbilt University eye exams showed further acuity improvement in OD to 20/40-2 and OS to 20/60+2 but in April 2016, the subretinal stem cells OS were mistakenly interpreted to be a choroidal neovascular membrane and an intravitreal injection of Avastin was administered. In May 2016, the patient's visual acuity was OD 20/40-2, ETDRS 20/40-1, and the visual acuity OS had declined to 20/100+1, ETDRS 20/80+2. In October 2016, the visual acuity as measured at Vanderbilt University was 20/25 OD and 20/40+2 OS.

In August 2017, the patient underwent Next Generation Sequencing (NGS) of 280 genes associated with known retinal dystrophies. The results were considered inconclusive with the presence of a heterozygous mutation in the ABCA4 gene and a heterozygous deletion of exon 3 in the NPHP4 gene. There was no apparent abnormality of EFEMP1. EFEMP2 (known to share genetic homology with EFEMP1) was not tested. Toto., *et al.* have reported that five of seven family members of a known Malattia Leventinese cohort failed to reveal the typical mutation and that other genes may have a role in the disease [6].

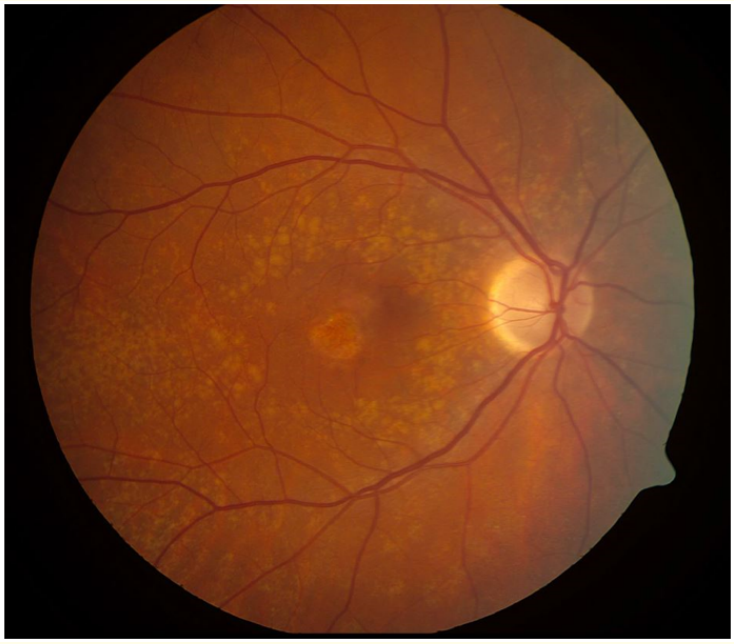

Figure 3: *Postoperative fundus photograph OD.*

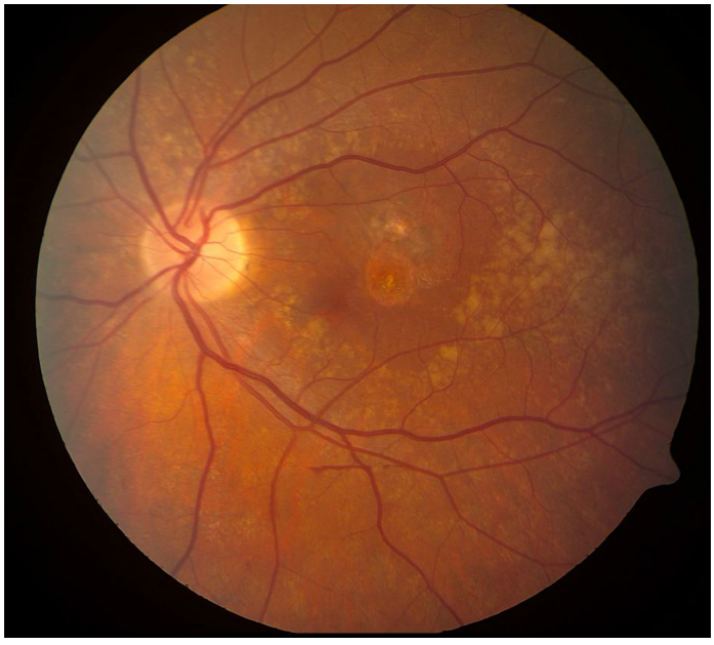

Figure 4: *Postoperative fundus photograph OS.*

Discussion

This patient with hereditary macular degeneration, clinically diagnosed as Malattia Leventinese, experienced bilateral acute visual loss resulting in the loss of his driver's license, the loss of his job and permanent visual disability status including training with a "white cane".

At 53 years of age, he chose to participate in SCOTS and underwent retrobulbar, subtenons and intravitreal injection of autologous BMSC OD and vitrectomy with subretinal injection and subtenons injection of BMSC OS.

Three days after treatment, the visual acuity improved to 20/60+1 OD and 20/60+2 OS. 14 months postoperatively, the visual acuity was 20/25 OD and 20/40+2 OS. The patient reported expanded independence regaining the ability to read, obtain a drivers license, a job, and relinquishing his status as a visually disabled person. It also led to his political involvement in advocacy for stem cell treatments including meetings with United States Congressional leadership and input on new healthcare legislation.

Potential means by which the visual improvement occurred may include actions of exosomes (nano-sized extracellular vesicles) micro ribonucleic acid (miRNA), transfer ribonucleic acid species and fragments (tRNA) as well as other paracrine elements [9]. The presence of growth factors including brain derived neurotrophic factor (BDNF) [10], nerve growth factor and glial cell line-derived neurotrophic factor (GDNF) [11] may have a roll in increasing remaining photoreceptors, outer nuclear, outer plexiform, inner nuclear and inner plexiform layer function. Mitochondrial transfer from mesenchymal stem cells (MSC) to injured cells has been shown in other studies [12]. Neuronal transdifferentiation of BMSC cells, specifically CD34+ cells to NeuN positive cells, has also been documented in patients treated in SCOTS [13]. *In-vivo* neuronal transdifferentiation of BMSC has been established by Vaquero and Zurita after these MSC were transplanted into injured spinal cord [14]. Immune modulation may also play a role in reducing any local inflammation; BMSC have been shown to modulate inflammatory activity and assist in nervous system recovery after spinal cord injury [15].

Conclusions

This patient with long-term macular degeneration, presumed Malattia Leventinese, experienced significant improvement in his visual acuity and visual field examinations following treatment with autologous BMSC as proscribed in the SCOTS protocols. Autologous BMSC may prove valuable in the treatment of hereditary maculopathies such as Malattia Leventinese, as well as other retinal and macular conditions.

Patient Consent to Publication

The patient provided written consent for the manuscript publication.

Funding

None.

Conflict of Interest

None.

Author's Contribution

Jeffrey Weiss designed the study, performed the treatment, provided follow up, wrote and edited the manuscript. Steven Levy designed the study, provided study support, wrote and edited the manuscript. Both authors attest that they meet the current ICMJE criteria for authorship.

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