Autologous Bone-Marrow Derived Stem Cells in the Treatment of “Untreatable” Optic Nerve and Retinal Conditions

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Abstract

The Stem Cell Ophthalmology Treatment Study or SCOTS is an Institutional Review Board (IRB) approved clinical study focused on diseases of the retina and optic nerve. The study uses autologous Bone Marrow Derived Stem Cells (BMSC) provided to the eye most typically with a combination of retrobulbar, subtenons and intravenous injections depending on the Arm of the study. The BMSC is obtained through centrifugation of aspirated bone marrow using minimal manipulation in compliance with United States Food and Drug Administration (FDA) guidelines.

SCOTS has published results in several papers [1-5] Non-Arteritic Ischemic Optic Neuropathy (NAION) has shown statistically significant improvement in our recent paper: 73.6% of eyes gained vision with an average logMAR improvement of 22.74%. In eyes that improved, the gain of vision on LogMAR was 36.7%. Lebers Hereditary Optic Neuropathy (LHON) has shown gains of up to 35 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. Patients with maculopathy, Serpiginous Retinopathy and Optic Neuropathies have improved sometimes very dramatically: 20/4000 to 20/30+, 20/800 to 20/40-, 20/350 to 20/150, 20/70 to 20/15. Results in our pending paper on Retinitis Pigmentosa show a statistically significant benefit to vision in about 45% of eyes with an average improvement in LogMAR vision of over 40% - the first time that a treatment has shown benefit in this disease.

In the course of the study approximately many different ocular conditions have been treated with documented improvements in most. Retinal diseases have included Age-Related Macular Degeneration (AMD), Stargards Disease, Retinitis Pigmentosa, Ushers, Cone-Rod Dystrophy, Presumed Ocular Histoplasmosis (POHS), Serpiginous Retinopathy. Optic neuropathies have included Glaucoma, NAION, Optic Atrophy from compressive, toxic, inflammatory, autoimmune and idiopathic causes, LHON, Dominant Optic Atrophy as well as other optic neuropathies. In this paper we summarize the initial publications in SCOTS which strongly support the use of BMSC in ophthalmic disease.

Keywords: Bone Marrow Derived Stem Cells (BMSC); Non-arteritic Ischemic Optic Neuropathy (NAION); Retinitis Pigmentosa (RP); Glaucoma; Age Related Macular Degeneration (AMD); Stargards Disease; Lebers Hereditary Optic Neuropathy (LHON); Ushers;Optic Atrophy; Cone-Rod Dystrophy

Introduction

SCOTS, the Stem Cell Ophthalmology Treatment Study, is the largest National Institutes of Health registered stem cell study currently recruiting in ophthalmology. The original protocol is being continued as the Stem Cell Ophthalmology Treatment Study II (SCOTS 2): NCT Number 03011541. Both SCOTS and SCOTS 2 (referred together as SCOTS) are Institutional Review Board (IRB) approved and FDA compliant. SCOTS is a patient supported, open label, non-randomized, efficacy study. All patients accepted receive active treatment and no placebo or sham approach is utilized. Bone marrow derived stem cells (BMSC) are obtained using an FDA cleared medical device to process bone marrow aspirated from both posterior iliac crests. An average of 1.2 billion total nucleated cells (TNC) is typically obtained which is then used for patient treatment.

Methods

Inclusion criteria for SCOTS provide that patients:

- Have disease or damage affecting the retina or optic nerve unlikely to improve or is progressive.
- Have vision that is less than or equal to 6/12 (20/40) best corrected central visual acuity or an abnormal visual field.
- If receiving eye surgery be at least 3 months post-op and stable.
- If receiving medical therapy (pharmacologic treatment) for a retinal or optic nerve disease be stable on that treatment and without likelihood of visual improvement (for example, glaucoma with intraocular pressure stable on topical medications but visual field damage).
- Have potential for improvement with BMSC treatment and unlikely to be harmed by the procedure.
- Patients must be at least 18 years old.
- Patients must be medically approved by a physician to undergo anesthesia and the procedure. This includes a history and physical, lab testing, EKG and Chest X-ray.

Exclusion criteria include:

- Patients who are not able to undergo a satisfactory ophthalmologic examination for initial evaluation and subsequent follow-up exams.
- Patients unable to provide informed consent.
- Patients at risk to their general health or to the eyes and visual function by potentially undergoing the procedure.

The SCOTS clinical trial consists of three treatment arms. These are not randomized – the treatment arm is chosen by the Principal Investigator taking into account the visual acuity, cause of visual damage, area of eye that is diseased or damaged, prior ocular surgery and medical risk factors. Bilateral treatment may be provided if both eyes meet eligibility requirements. Approximately 140 cc of bone marrow is placed in an FDA cleared medical device and the bone marrow aspirate is separated into a stem cell concentrate typically consisting of an average of 1.2 billion total nucleated cells (TNC). The stem cell concentrate includes mesenchymal stem cells in a total of about 14 cc of concentrate. The following injection techniques are used in various combination for the three Arms:

- Retrobulbar injection consists of injection of 3 cc of concentrate in the retrobulbar area behind the globe.
- Subtenon injection consists of 1 cc of concentrate injected in the subtenons space adjacent to the eye.
- Intravitreal injection consists of approximately 0.05 cc of concentrate injected within the vitreal cavity.
- Subretinal injection consists of approximately 0.1 cc of concentrate injected beneath the retina following vitrectomy.
- Intra-optic nerve injection consists of approximately 0.1 cc of concentrate injected within the optic nerve.
- Intravenous injection provides the remaining stem cell concentrate intravenously after the ocular injections have been delivered.

Arm 1 consists of BMSC fraction delivered by retrobulbar, subtenons and intravenous infusion. Arm 1 is now the standard approach being provided in SCOTS 2. Retrobulbar placement allows movement of stem cells and released exosomal products into the eye, likely through the posterior ciliary arteries. Subtenons provides a depot of stem cells that can enter the eye and release exosomal products. BMSC provided intravenously have approximately 30 times the ability of any other type of stem cell to move through the pulmonary capillary bed and reach the circulation through the eyes. We believe prior placement of BMSC in the orbit provides chemotactic stimulus for the circulating stem cells, augments their attraction to the eyes and the overall effectiveness of the stem cells. The risks of these injections is extremely small - on the order of 0.00008 to 0.00014 for misplacement. Arm 1 appears to be as effective as Arm 2 or 3 in most conditions and avoids the risks of intraocular injection or vitrectomy surgery. Patients with ophthalmic conditions which preclude safe or effective utilization of intravitreal injection of concentrate, such as the presence of silicone oil or prior glaucoma surgery, may also be offered Arm 1.
Arm 2 consists of the administration of retrobulbar, subtenons and intravitreal BMSC fraction followed by intravenous infusion. Patients meeting inclusion criteria with visual acuity typically of 20/200 or worse in retinal conditions or optic neuropathy may be offered Arm 2.

Arm 3 consists of the eye with better visual acuity receiving the same treatment as Arm 1 or Arm 2, and the eye with more extensive visual acuity loss, 20/200 or worse, receiving a core pars plana vitrectomy with injection of subretinal or intra-optic nerve concentrate followed by the infusion of intravenous stem cells. Patients with only one functional eye are not eligible for Arm 3.

For all patients treated in SCOTS post-operative eye exams are required at 1, 3, 6 and 12 months following treatment and must be provided to the Principal Investigator and Study Director. The focus of treatment in SCOTS is the actual cellular destruction or cellular impairment causing visual loss rather than the instigating disease. Unlike typical pharmaceutical drug development in which specific drug targets involved in the disease process are identified and treated, the use of BMSC is a regenerative approach for tissue repair that allows the treatment of multiple retinal and optic nerve diseases. This includes situations where visual loss may be due to more than one disease such as AMD and glaucoma. Identified mechanisms of action include cellular transdifferentiation including neuronal transdifferentiation; NeuN positive cells have been identified associated with CD34 cells after intravitreal injection of BMSC. Additional mechanisms include exosomal release of messenger ribonucleic acid (mRNA), release of Nerve Growth Factor, neurotrophic factors, and mitochondrial transfer via cytoplasmic bridges. These are the patient’s own stem cells, known as autologous stem cells, and therefore no immunosuppression is necessary. Because BMSC are not embryonic or derived from embryonic stem cells, teratoma formation is not a concern and there is no moral or ethical controversy.

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

Summary of Publications

We have previously reported the treatment with BMSC of 2 patients with optic nerve disease [1,2]. The first patient was a 32 year-old female with a 5 year history of legal blindness secondary to idiopathic optic atrophy. She had been followed by the Wilmer Eye Institute at the Johns Hopkins Hospital. Pre-treatment best-corrected visual acuity was 20/800 OD and 20/4000 with severe visual field loss. Four months following treatment in SCOTS the visual acuity improved to 20/100 OD and 20/40 OS and visual fields also improved in each eye. There was a second treatment in SCOTS approximately 13 months after the first; at approximately 2 years following the initial treatment the visual improvements reached 20/40-2 OD and 20/30+2 OS.

A second 54 year-old female patient with optic neuropathy, possibly from neuromyelitis optica, was followed at the Nationwide Children’s Hospital and the Ohio State University. The visual acuity was 20/350 OD and 20/70 OS prior to treatment with severe visual field defects OU. At the six month post-operative visit the visual acuity had improved to 20/150 OD and 20/15 OS with improvement noted in the visual fields OU.

In another paper, five patients with Lebers Hereditary Optic Neuropathy (LHON) treated in SCOTS were reported. Post-operatively there were visual acuity gains of up to 35 letters when measured on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Snellen acuity improved from hand motion to 20/200 and from counting fingers to 20/100. Visual field improvements were noted. Macular and optic nerve head nerve layers were typically noted to thicken [3].

We recently published a paper on a group of patients with Non-Arteritic Ischemic Optic Neuropathy (NAION) treated in SCOTS. In that group 80% of patients experienced improved binocular vision (p = 0.029) and 20% remained stable. In assessing individual eyes, 73.6% of eyes gained vision (p = 0.019) and 15.9% were stable in the follow up period. The average improvement in Snellen acuity was 3.53 lines of vision per eye. When measured with logMAR there was an average improvement per treated eye of 22.7% and in the eyes that improved, the average improvement was 36.7% on LogMAR [4]. The average gain in logMAR in treated eyes was 0.364 (p = 0.0089). These findings represent the first time that any treatment has been shown to be of benefit in this chronic and blinding optic neuropathy.
The SCOTS procedure has also proven useful as a treatment for retinal conditions. A 77 year old man with long-standing visual loss from Serpiginous Choroidopathy enrolled in SCOTS [5]. Following treatment, the patient’s best corrected Snellen acuity improved from 20/100 to 20/60-2 in the right eye and from 20/60 to 20/20-3 in the left eye. Within 2 weeks of the procedure there was a 4 line improvement in his visual acuity, sufficient to obtain a driver’s license. The ETDRS visual acuity continued to improve over the succeeding 8 months and the OCT macular volume increased.

Drusen expressing maculopathies and retinopathies including AMD have also improved following treatment in SCOTS. A 53 year old legally blind patient diagnosed with a drusenoid maculopathy, likely hereditary, underwent retrobulbar, subtenons and intravitreal injection of autologous BMSC (Arm 2) OD and vitrectomy with subretinal injection and subtenons injection of BMSC (Arm 3) OS. Preoperative exam showed visual acuity OD of 20/400 and in OS of 20/2000. 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 driver’s license, a job and relinquishing his status as a visually disabled person.

In our recently accepted journal article reporting on Retinitis Pigmentosa (RP) approximately 64% of patients showed increases in binocular vision averaging just over 10 Snellen lines. Approximately 45% of eyes showed visual improvement and most all remaining eyes avoided further loss in the follow up period. Benefitting eyes showed over 40% improvement on logMAR scale. This is the first time that any treatment has shown statistical improvement in vision for this otherwise untreatable hereditary retinopathy.

We are presently analyzing data from treated patients diagnosed with Usher’s Syndrome, Stargardt’s disease and Age-related Macular Degeneration (AMD). The overall data appear promising and we expect statistical significance of visual improvement to be shown in these conditions as well.

Conclusion

The SCOTS clinical trial has demonstrated that BMSC separated using certain proprietary techniques and provided through ocular injections and intravenous delivery can provide visual acuity improvement in multiple retinal and optic nerve diseases. The causes of visual impairment in ophthalmic disease can be divided into three broad categories: loss of media clarity impairing proper light transmission, disruption of cellular functioning of the photoreceptor layer, and transmission issues of the nervous tissue of the eye. Resolving media issues with surgical approaches is well established – these include corneal, cataract, vitreous and retinal surgeries. Interruption of ongoing processes that may ultimately result in cellular damage such as addressing intraocular pressure in glaucoma, stopping subretinal bleeding in AMD, or efforts to maintain proper capillary circulation in diabetes are staples of care. However once cellular damage or loss is present, conventional and preventative approaches typically no longer resolve the resulting visual impairment. The visual improvements achieved using BMSC result from global resolutions of cellular damage including improvement in cellular function and likely partial replacement of damaged or lost cells. Mechanisms are still being identified and include cellular transdifferentiation including neuronal transdifferentiation, secretion of mRNA, release of nerve growth factor or other neurotrophic factors and mitochondrial transfer via cytoplasmic bridges to other cells.

The SCOTS clinical trial will continue to publish results for groups of patients with other specific diseases including AMD, Stargardts and Ushers. Our expectation is that results will similarly show statistically significant and meaningful visual improvements. SCOTS is the only actively recruiting ophthalmologic study with peer-reviewed publications that confirm statistical significance of the treatment approach in both optic nerve and retinal disease. Through continued patient recruitment and publication of results we hope to help establish the clinical value of BMSC in the treatment of otherwise irreversible ocular disease.

Bibliography


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