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ALSUntangled No. 27: Precision Stem Cell

The ALSUntangled Group

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ALSUntangled reviews alternative and off-label treatments for patients with ALS (PALS). Here, we examine the treatment offered at Precision Stem Cell, for which we have had more than 1100 requests (1). This is the first review that incorporates our new Table of Evidence (TOE, (2)).

Precision Stem Cell (PSC) is a clinic formerly in Gulf Shores, Alabama now in Bogota, Columbia. It is led by Jason Williams, a radiologist (3). He uses imaging techniques such as MRI, CT, fluoroscopy and ultrasound (4) to insert mesenchymal (meaning loosely packed in a gelatinous ground substance such as fat, umbilical cord or bone marrow) stem cells (MSCs) into patients with various ailments. This is primarily marketed toward athletes as a way to help them recover faster from musculoskeletal injuries (5).

Protocol(s) for PALS

Williams began administering MSC transplant therapy to PALS in early 2012, after being approached to treat a former college football coach (6,7). He says he reviews outside records to validate the ALS diagnosis (7). On 1 April 2013 Williams described his ALS protocol to us as follows: "I harvested fat from a minimally invasive liposuction. We process(ed) the fat within a Medi-Kahn Lipokit and Maxstem system. This system had been studied with reproducible results demonstrating an average of about 1 million stem cells per ml. We did not actually measure this ourselves. We would usually use 30–50 ml of fat, estimating 30–50 million ASCs. We did incubate this (stromal fraction) with a small amount of selegiline. I am not sure how useful this really was. It was initially done with the idea of generating neural-like cells. But as I described, regeneration of neural cells probably does not occur" (7). Williams apparently obtained the idea for using selegiline from a study in which adipose-derived MSCs were differentiated into neuron-like cells in this manner (8). Following selegiline treatment, the stromal fraction was injected into the extremity muscles and the spinal fluid of the person who donated the fat. No safety or efficacy outcome measures appear to have been objectively or systematically monitored. This description is similar to what two independent groups reported in their own reviews of PSC in early 2013 (9,10).

Over the remainder of 2013, Williams apparently changed his protocol (7). On 20 August 2013 he told us that he had started to use umbilical-derived cells from donors without ALS, was working with "gene therapy", and was testing image guided injections into the spinal cord and nerve roots (7). Our email requests for additional details on these changes have largely gone unanswered (7).

With regard to the gene therapy, the PSC website notes a partnership with a company called Neuralgene (6). The Neuralgene website states that they use a virus (AAV) to deliver various genes to various tissues for patients with different diseases (11). For ALS, the website says: 'The AAV9 viral vector delivers multiple genes, which include Factor H (a regulator of complement activity), neural growth factors and regulators of TDP-43, to the neural cells' (12). The status of Neuralgene's ALS product development program is unclear; animal studies of this gene therapy were reported to begin in May 2013 (12) but the website also claims: 'Neuralgene has initiated initial human testing in it's gene therapy for ALS' (11). Typically, animal studies would be completed before human testing begins. A PubMed search identified no published studies on Neuralgene protocols in animals or humans and there are no Neuralgene trials listed on ClinicalTrials.gov. Williams is listed as the CEO and director of R&D for Neuralgene (13).

On 24 September 2014 Williams wrote: "We are not doing much with stem cells anymore, mostly just a little orthopedic work….we tried aav, vegf, gdnf, igf2, but nothing exciting" (7). ALSUntangled has been unable to obtain any additional details. According to the PSC website (6) and an email from Williams dated 7 October 2014, some form of MSC treatment is still being offered to patients with ALS (7).

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ALSUntangled agrees with two specific and serious concerns raised by prior independent reviews of PSCs ALS protocols (9,10) – lack of quantification of exactly what is being injected into PALS, and lack of objective outcome measures. There also is no significant information available regarding subsequent, seemingly major changes to the protocol.

Theoretical method of action in ALS

Neuroinflammation (14) and growth factor deficiencies (15) are both present in PALS and have been the targets of many previous and ongoing trials. MSCs secrete a variety of bioactive agents that can modulate inflammation and increase growth factors (16,17). Transplantation of MSCs into a mouse model of ALS resulted in significant, though transient, increases in several growth factors in the spinal cord (18). ALSUntangled has found no study showing that MSCs alter neuroinflammation or growth factor levels in PALS. ALSUntangled assigns a TOE 'Mechanism' grade of B based on this information (Table I).

Many questions about MSCs as a therapeutic tool have yet to be answered. The optimal source of MSCs is still unclear; one study suggests that adipose-derived MSCs may be more potent modulators of inflammatory pathways than bone marrow-derived MSCs (19). Autologous (taken from and given to the same person) MSCs may have the genetic or metabolic defects that are contributing to the ALS in the first place, but MSCs from another person would likely need to be administered with immunosuppression. It is as yet unclear whether any pre-treatment of MSCs (with drugs, viruses or genes) will make them work better. The optimal dose, transplant location, and frequency of transplants have not to date been defined. In our opinion, these questions can only be answered by carefully designed studies featuring transparent and reproducible treatment protocols that include verification of the substances being transplanted and objective outcome measures.

Relevant data in pre-clinical ALS models

While PSC does not appear to have published any pre-clinical studies, several other groups have shown that MSC transplants can delay loss of motor function and/or prolong survival in SOD1 mutation based mouse models of ALS (18–26). These include studies using MSCs from different sources, with different pre-treatments, injected into different places in the animals, both before and at disease onset. It is not clear from reading these studies that one protocol is working better than another. All these studies have at least one flaw according to published guidelines (27). ALSUntangled assigns a TOE 'Pre-Clinical Models' grade of C based on this information (Table I).

Table I. TOE Grades (2) for PSC's ALS treatment.

	Grade	Explanation
Mechanism	B	MSC transplants can alter spinal cord growth factors in an animal model of ALS
Pre-clinical	C	Multiple flawed peer-reviewed publications report benefits of MSC transplants in ALS models
Cases	D	Subjective reports of benefit from PSC's ALS protocols without independent confirmation of diagnosis or improvements
Trials	U	No trials of PSC's ALS protocols
Risks	C	At least three of 25 PALS identified as having PSC treatment had side-effects (none had hospitalizations or deaths)

Relevant data in PALS

There are no published trials of PSC's protocols for PALS. There are encouraging preliminary data from other groups performing MSC trials in PALS (28), but these were obtained using different protocols and thus are not directly relatable to PSC. ALSUntangled assigns a TOE 'Patient Trials' grade of U based on this information (Table I).

According to Williams (7), he has treated 25 PALS, and "I think about one-third demonstrated improvement, but it was usually short term (less than three months). We did have three patients that have reported continued maintenance of improvement at 9–12 months out" (7). Williams provided us with contact information for four PALS whom he considers his "best successes". ALSUntangled contacted these PALS and heard back from two of them. Both reported improved limb movements after the transplants, and one reported improved breathing. We have records confirming an ALS diagnosis in one of these, but do not have records confirming improvements in either of them.

Within the PatientsLikeMe online community we found two PALS who reported having MSC transplants at PSC. The one whose profile is public reported significant improvements in motor function, but which lasted less than two weeks from the transplant (29). Google search identified no additional PSC-treated PALS reporting on efficacy.

ALSUntangled assigns a TOE 'Patient Case Reports' grade of D based on this information (Table I).

Risks, costs

In terms of side-effects, Williams reported: "We had one patient that had leg pain (radicular type symptoms) lasting about two weeks. Several other patients had the same symptoms lasting 2–3 days" (7). We have not found evidence of other side-effects from PSC treatments in PALS. Assuming 'several' means at least two, ALSUntangled assigns

a TOE 'Risks' grade of C based on this information (Table I). A recent, detailed review of published studies of MSC transplants into patients with ALS likewise suggests that this procedure can be carried out safely under controlled conditions (28). However, there is a potential risk for serious, even deadly, infections whenever injections are performed into the spinal fluid. This is highlighted by the recent outbreak of fatal fungal infections associated with epidural injections of methylprednisolone from a compounding pharmacy (30). Injections into the spinal cord itself are even more dangerous, with theoretical risks including intractable pain, loss of bowel and bladder function, spinal shock and death.

In terms of costs, most PALS were charged between $13,000 and $15,000 for MSC transplant at PSC (7). Williams reported that six patients were treated free of charge (7). Insurance is unlikely to cover any part of PSC ALS treatments.

Conclusions

At ALSUntangled our goal is to provide guidance on the mechanism, pre-clinical data, anecdotal evidence, trials and risks of various alternative treatment options. Our goal is not to challenge the rights of PALS to pursue these options. Along these lines, MSC transplants in general have a promising mechanism, good pre-clinical data in ALS models and appear reasonably safe when performed with approved standardized protocols, proper oversight, and monitoring. However, the specific protocols used at PSC for PALS are poorly detailed, appear variable in terms of the sources of MSCs being used, the ways these are being modified and the places where these are being inserted, have no provision for confirming the material being inserted, and have only subjective and usually brief improvements associated with them.

ALSUntangled strongly supports further study of MSC in PALS, but only with transparent, reproducible protocols that include confirmation of transplanted material and objective outcome measures. At this time, it does not appear to us that PSC is meeting these criteria.

The ALSUntangled Group Currently Consists of the following members: Eric Valor, Richard Bedlack, Colin Quinn, Chafic Karam, Alex Sherman, Lyle Ostrow, Orla Hardiman, Terry Heiman-Patterson, Laurie Gutmann, Mark Bromberg, Gregory Carter, Edor Kabashi, Tulio Bertorini, Tahseen Mozaffar, Peter Andersen, Jeff Dietz, Josep Gamez, Mazen Dimachkie, Yunxia Wang, Paul Wicks, James Heywood, Steven Novella, L. P. Rowland, Erik Pioro, Lisa Kinsley, Kathy Mitchell, Jonathan Glass, Sith Sathornsumetee, Hubert Kwiecinski, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlayne Jackson, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorenson, Christen Shoesmith, Steven Nash, Nicholas Maragakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, Dan Pastula, Gleb Levitsky, Mieko Ogino, Jeffrey Rosenfeld, Efrat Carmi, Merit Cudkowicz, Christina Fournier, Paul Barkhaus, Brett Morrison, Lorne Zinman, Craig Oster.

Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

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