Autologous Muscle Derived Cells for Treatment of Stress Urinary Incontinence in Women

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Purpose: We assess the 12-month safety and potential efficacy of autologous muscle derived cells for urinary sphincter repair (Cook MyoSite Incorporated, Pittsburgh, Pennsylvania) in women with stress urinary incontinence.

Materials and Methods: Pooled data from 2 phase I/II studies with identical patient selection criteria and outcome measures were analyzed. Enrolled patients had stress urinary incontinence refractory to prior treatment and no symptom improvement during the last 6 months. Patients received intrasphincter injection of 10 (16), 50 (16), 100 (24) or 200 $\times$ 10^6 (24) autologous muscle derived cells for urinary sphincter repair, derived from biopsies of each patient's quadriceps femoris. The primary outcome measure was safety, determined by incidence and severity of adverse events. Potential efficacy was measured by changes in 3-day voiding diaries, 24-hour pad tests, and UDI-6 and IIQ-7 scores.

Results: A total of 80 patients underwent injection of autologous muscle derived cells for urinary sphincter repair, and 72 completed diaries and pad tests at 12-month followup. No adverse events attributed to autologous muscle derived cells for urinary sphincter repair were reported. Higher dose groups tended to have greater percentages of patients with at least a 50% reduction in stress leaks and pad weight at 12-month followup. All dose groups had statistically significant improvement in UDI-6 and IIQ-7 scores at 12-month followup compared to baseline.

Conclusions: Autologous muscle derived cells for urinary sphincter repair at doses of 10, 50, 100 and 200 $\times$ 10^6 cells appears safe. Efficacy data suggest a potential dose response with a greater percentage of patients responsive to higher doses.

Key Words: transplantation, autologous; urinary incontinence, stress; myoblasts, skeletal; muscle cells

Abbreviations and Acronyms

AMDC-USR = autologous muscle derived cells for urinary sphincter repair

IIQ-7 = Incontinence Impact Questionnaire short form

SUI = stress urinary incontinence

UDI-6 = Urogenital Distress Inventory short form

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Study received ethics board approval.

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STRESS urinary incontinence, the involuntary leakage of urine during activities that increase abdominal pressure (eg coughing, sneezing, physical exercise), affects up to 35% of adult women.[1] This condition is caused by pelvic floor weakness, urethral hypermobility and/or sphincter deficiency. Interventional therapies may be necessary when first line conservative management such as pelvic floor muscle training fails to provide adequate symptom relief. Sling procedures and bladder

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neck suspensions can be effective. However, complications of urinary retention, worsening urgency symptoms and erosion/extrusion of mesh have been reported.[2] Injection of urethral bulking agents is less invasive, but lacks durability and has been associated with degradation/reabsorption, migration, bladder outlet obstruction and hypersensitivity reactions.[3]

A potential alternate therapy is the use of autologous muscle progenitor cells, which are isolated from skeletal muscle biopsies and expanded ex vivo before injection into the urethral sphincter. This approach may benefit patients with SUI by augmenting sphincter function. Two previous studies assessed AMDC-USR in women with SUI.[4,5] A pilot study tested 18 to 22 $\times$ 10^6 AMDC-USR in 8 patients and another assessed doses ranging from 1 to 128 $\times$ 10^6 AMDC-USR in 38 patients. In both studies the patients could opt to receive a second treatment of AMDC-USR and the use of AMDC-USR appeared safe. Additionally, the dose ranging study results suggested greater efficacy for patients who received 2 AMDC-USR treatments of at least 32 $\times$ 10^6 cells.[5] In this report we describe pooled data from 2 open label studies conducted concurrently that were designed to collectively assess the 12-month safety and potential efficacy of 4 doses of AMDC-USR for the treatment of SUI in 80 women.

METHODS

Two phase I/II studies were conducted to assess the 12-month safety and potential efficacy of AMDC-USR for the treatment of SUI in women. Both studies were performed in accordance with the Declaration of Helsinki. Study protocols were approved by the ethics board at each site before study initiation and written informed consent was obtained from all patients. Both studies were conducted concurrently and intended to be evaluated together. Each protocol specified the same patient selection criteria and outcome measures.

Study 1 was a dose escalation study conducted between October 2008 and November 2011 at 3 investigative sites in the United States and Canada (ClinicalTrials.gov Identifier: NCT00847535). The study protocol, designed to test 10, 50 and 100 $\times$ 10^6 AMDC-USR in 48 patients (16 patients per group), was approved by the FDA (Food and Drug Administration) and Health Canada. In an amendment approved by the FDA, study 1 was expanded to include 16 additional patients to receive 100 or 200 $\times$ 10^6 AMDC-USR (8 patients per group) at 2 U.S. investigative sites. A separate protocol to test 200 $\times$ 10^6 AMDC-USR in 16 patients was approved by Health Canada and was conducted at 2 Canadian investigative sites from June 2010 to September 2012 (study 2, ClinicalTrials.gov Identifier: NCT01008943).

Inclusion criteria were women age 18 years or older with SUI refractory to prior treatment with no improvement of SUI symptoms for at least 6 months before enrollment (see Appendix). Each patient underwent a needle biopsy of the quadriceps femoris under local anesthesia during an outpatient office procedure. The biopsy tissue was placed in a hypothermic solution and shipped at 2 to 8C to a central cell processing facility at Cook MyoSite Incorporated.

Manufacturing and testing were conducted using proprietary procedures based on global standards for aseptic biological product manufacturing. A subpopulation of muscle derived cells was expanded in culture. Products were formulated to the cell number dose in a total volume of 2 ml with biopreservation media and cryopreserved at −80C.

Before release all products underwent complete quality control testing and inspection. The percentage of myogenic cells in the product, as identified through skeletal muscle marker expression, was 86% $\pm$ 14%. The other cells were primarily fibroblasts.

Frozen AMDC-USR product was supplied to the investigator. The product was thawed and diluted to a total volume of 4 ml with 2 ml of 0.9% saline. Each patient received a single treatment of AMDC-USR during an outpatient office procedure. Local anesthetics were generally used. Intrasphincter injections (at least 8 injections of about 0.5 ml each) were made into the mid urethral complex, with needle lengths allowing cell injection into the region of the external striated sphincter. Techniques used included cystoscope guided transurethral injection (modified Williams Cystoscopic Injection Needle, Cook Medical, Bloomington, Indiana), cystoscope guided periurethral injection (22 gauge needle, brand not specified) and transurethral injection with the SUI Injection Needle (Cook Medical), a device containing 3 simultaneously deployed needles.

The primary objective of the studies was to assess safety by the incidence and severity of adverse events. Secondary objectives were to assess efficacy via 3-day voiding diaries, 24-hour pad tests, and the validated patient questionnaires UDI-6 and IIQ-7.[6] Diaries and pad tests were completed at baseline and at 1, 3, 6 and 12 months after treatment. UDI-6 and IIQ-7 were completed at baseline and at 6 and 12 months after treatment.

The percentage of patients with at least a 50% reduction from baseline stress leaks as measured by 3-day diary, the percentage with at least a 50% reduction from baseline pad weight, the percentage reporting no stress leaks over 3 days and the percentage with negative pad tests (less than 1.3 gm pad weight) were determined from 12-month data. If no outcome data were available for a patient at a given point, the patient was excluded from the calculation for that particular outcome measure and point. Patients reporting no stress leaks during 3 days at baseline were excluded from the analysis of stress leak data since no improvement could be detected by diary reported stress leaks. Stress leak and pad test data were also assessed for the subset of patients with at least 3 diary reported stress leaks during 3 days and at least a 3 gm 24-hour pad weight at baseline.

Data were analyzed using SAS® version 9.3. Continuous variables were summarized as mean $\pm$ standard error (range), ordinal variables were summarized as median (range) and categorical variables were summarized