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Research Paper

Safety and Potential Effect of a Single Intracavernous Injection of Autologous Adipose-Derived Regenerative Cells in Patients with Erectile Dysfunction Following Radical Prostatectomy: An Open-Label Phase I Clinical Trial

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ABSTRACT

Background: Prostate cancer is the most common cancer in men, and radical prostatectomy (RP) often results in erectile dysfunction (ED) and a substantially reduced quality of life. The efficacy of current interventions, principal treatment with PDE-5 inhibitors, is not satisfactory and this condition presents an unmet medical need. Preclinical studies using adipose-derived stem cells to treat ED have shown promising results. Herein, we report the results of a human phase 1 trial with autologous adipose-derived regenerative cells (ADRCs) freshly isolated after a liposuction.
Methods: Seventeen men suffering from post RP ED, with no recovery using conventional therapy, were enrolled in a prospective phase 1 open-label and single-arm study. All subjects had RP performed 5–18 months before enrolment, and were followed for 6 months after intracavernosal transplantation. ADRCs were analyzed for the presence of stem cell surface markers, viability and ability to differentiate. Primary endpoint was the safety and tolerance of the cell therapy while the secondary outcome was improvement of erectile function. Any adverse events were reported and erectile function was assessed by IIEF-5 scores. The study is registered with ClinicalTrials.gov, NCT02240823.
Findings: Intracavernous injection of ADRCs was well-tolerated and only minor events related to the liposuction and cell injections were reported at the one-month evaluation, but none at later time points. Overall during the study period, 8 of 17 men recovered their erectile function and were able to accomplish sexual intercourse. Post-hoc stratification according to urinary continence status was performed. Accordingly, for continent men (median $IIEF_{inclusion} = 7$ (95% CI 5–12), 8 out of 11 men recovered erectile function ($IIEF_{6months} = 17$ (6–23)), corresponding to a mean difference of 0.57 (0.38–0.85; $p = 0.0069$), versus inclusion. In contrast, incontinent men did not regain erectile function (median $IIEF_{1/3/6\ months} = 5$ (95% CI 5–6); mean difference 1 (95% CI 0.85–1.18), $p > 0.9999$).
Interpretation: In this phase I trial a single intracavernosal injection of freshly isolated autologous ADRCs was a safe procedure. A potential efficacy is suggested by a significant improvement in IIEF-5 scores and erectile function. We suggest that ADRCs represent a promising interventional therapy of ED following prostatectomy.
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1. Introduction

The promising potential of stem cell therapy for various diseases has been subject to much basic research and has attracted significant clinical interest. In clinical practice, however, such interventions remain largely experimental outside of bone marrow transplantation and autologous stem cell transplantation as related to chemotherapy (Dohner et al., 2015). Clinical implementation of stem cell treatment for erectile dysfunction (ED) represents a plausible candidate for such an approach. It

Abbreviations: RP, radical prostatectomy; ED, erectile dysfunction; PDE-5, phosphodiesterase-5; ADRC, adipose-derived regenerative cells; SVF, stromal vascular fraction; IIEF-5, international index of erectile function-5; EHS, erection hardness score; ICIQ-UI SF, incontinence questionnaire – urinary incontinence – short form questionnaire; BMI, body mass index; CFU-F, fibroblastoid colony forming units; NSAID, nonsteroidal antiinflammatory drug; LUTS, lower urinary tract symptoms.

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has been reported that mesenchymal stem cells from bone marrow or adipose tissue can correct ED in animal models (Gimble et al., 2012; Lin et al., 2012). Prostate cancer is the most common male cancer affecting 17% of all men (Chung and Gillman, 2014), of which approximately 25% receive a prostatectomy. Due to penile nerve injury, up to 86% of patients experience ED (Salonia et al., 2012; Tal et al., 2009; Weyne and Albersen, 2014) following prostatectomy. ED is defined as the consistent or recurrent inability to attain or maintain an erection sufficient for satisfactory sexual performance (*JAMA*, 1993; Montorsi et al., 2010). ED following prostatectomy is an important medical condition that substantially decreases quality of life of the afflicted men and their sexual partners (Litwin et al., 1998). Besides prostatectomy, ED risk factors include widespread diseases such as hypertension and obesity, but also medications such as β-blockers and anti-depressants, as well as major life-style factors like smoking and alcohol use cause ED (Shabsigh et al., 2005). Moreover, age is a risk factor; approximately one third of men in their forties report ED symptoms, while more than half of men over 60 years suffer from ED (Lewis et al., 2010). Although the prevalence and impact of ED remain substantial, current penile rehabilitation therapy following prostatectomy mainly consists of treatment with PDE-5 inhibitors or injection therapy, which have an unimpressive clinical efficacy around 27% or lower (Chung and Gillman, 2014; Weyne and Albersen, 2014; Weyne et al., 2015). This condition therefore presents a significant unmet medical need.

At the cellular level, ED is thought to be caused by neuro-vascular or hormonal dysfunction resulting in impaired vasodilatation of penile arteries (Salonia et al., 2012; Weyne and Albersen, 2014). When the natural nocturnal erection is lost, the penis tissue enters a chronic hypoxic state leading to vascular dysfunction (Mulhall et al., 2010). Adipose-derived regenerative cells (ADRCs, also referred to as stromal vascular fraction, SVF) are able to differentiate into vascular cells and neurons in vitro (Gimble et al., 2013; Lin et al., 2008; Zuk, 2010), and a large body of preclinical work shows a surprisingly good effect of ADRC injection into the corpora cavernosa (Lin et al., 2012). One human study reported improved erectile function using umbilical cord blood cells in 7 diabetic ED patients (Bahk et al., 2010). This latter study demonstrates proof of concept for the use of cell therapy in clinical ED treatment, even if the etiology of ED in diabetics may reflect less nerve injury as compared to patients after radical prostatectomy (RP) (Schauer et al., 2015). The safety of applying freshly isolated autologous ADRCs for non-homologous use in intracavernous injections has not previously been explored.

We here report safety and preliminary efficacy outcomes from a phase 1 clinical trial using autologous ADRCs for the treatment of ED in 17 men after radical prostatectomy.

2. Methods

2.1. Study Design and Eligibility Criteria

Study population (Fig. 1): Seventeen patients with ED after RP (3 open, 14 robot-assisted laparoscopic prostatectomies) were enrolled between May 2014 and September 2015 in this prospective, open-label, single-arm and single-center study. All subjects had RP performed at Odense University Hospital, Denmark, 5–18 months prior to enrolment. Inclusion criteria were: age >18 years. Clinical follow-up was required to show organ-confined prostate cancer without metastasis. Patients had to be sexually active before RP and expressing a wish to remain sexually active. Appropriate pharmacological intervention (PDE-5 or PGE1 analog) must have been tried and deemed insufficient to allow for inclusion. The participants were suggested to continue medication throughout the study period if they felt the slightest effect. Patients with no initial effect were encouraged to retry pharmacological treatment, to see if they had changed responder-status. Patients were told to continue other regular medications and pelvic physiotherapy during the trial.

Exclusion criteria: treatment with anticoagulants; insufficient subcutaneous fat; lack of sexual interest. We used the following

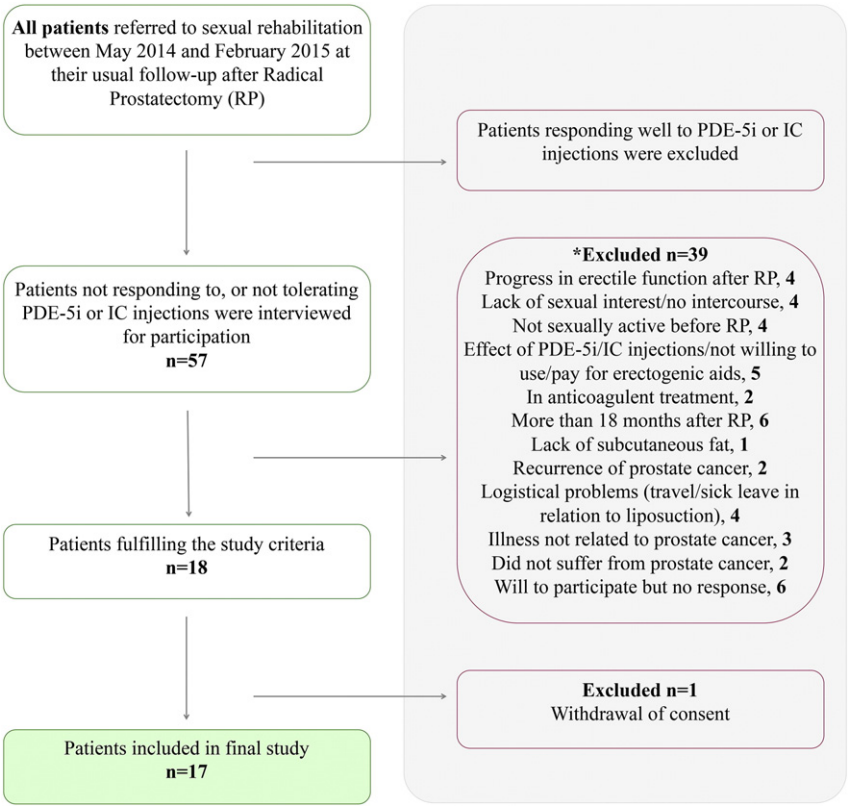

Fig. 1. Study overview. *Some patients were excluded based on several criteria. (IC:Intracavernous; RP:Radical Prostatectomy).