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LONG-TERM DURABILITY OF EFFICACY AND SAFETY OF REGENERATIVE TREATMENT OF MALE STRESS URINARY INCONTINENCE USING AUTOLOGOUS ADIPOSE-DERIVED REGENERATIVE CELLS

Hypothesis / aims of study

We created a novel treatment strategy to regenerate the urethral sphincter function, using autologous adipose-derived regenerative cells (ADRCs) without the need of cell culture (Fig.1). We published the short-term results of 11 male patients with stress urinary incontinence [1]. Although favourable efficacy and safety were confirmed at one year after treatment, durability of efficacy and safety should be confirmed in a long-term period. In the present study, we assessed the long-term durability of efficacy and safety in 14 male patients with stress urinary incontinence caused by urethral sphincter deficiency, who underwent periurethral injection of ADRCs and were followed longer than 4 years.

Study design, materials and methods

Fourteen male patients with persistent stress urinary incontinence after prostate surgery (radical prostatectomy, 12 patients; holmium laser enucleation of the prostate, 2 patients) underwent the periurethral injection of ADRCs and were followed longer than 4 year. After liposuction of 250 mL of adipose tissue from the abdomen, we isolated ADRCs from this tissue by using the CelutionTM system (Cytori Therapeutics Inc., San Diego, USA). Subsequently, these ADRCs and a mixture of stem cells and adipose tissue were transurethrally injected into the rhabdosphincter and submucosal space of the urethra, respectively. Unlike other cell therapies, this treatment is entirely autologous, does not require cell culture, and is performed as a single surgical procedure within 3 hours. Outcomes were mean daily leakage volume for 4 days assessed by a 24-hour pad test, maximum urethral closing pressure and functional profile length on urethral pressure profile, blood flow at the injected area evaluated by contrast-enhanced transrectal ultrasonography, and morphological changes of injected adipose tissue assessed by magnetic resonance imaging.

Measurement of urethral pressure, blood flow at the injected site and morphological change of injected adipose tissue were made until 12 months after treatment as previously reported [1]. Daily leakage volume was measured in a long-term follow-up at 1, 3, 6, 9, 12, 18, 24, 30, 36 and 48 months after the treatment.

Results

Mean follow-up period was 57.8 months (49 to 72 months). After injection, mean leakage volume/24-hours changed from 249.5 to 151.9g (mean of all patients). Urinary incontinence progressively improved up to 12 months after treatment in 11 of the 14 patients, and one patient with moderate incontinence achieved total continence at 14 weeks after injection. In the 11 patients who showed improvement, the mean daily leakage volume improved from 265.4 to 124.5 g at 4 years. In other 3 patients, mean daily leakage volume increased from 191.1 to 223.3 g. In the patients with improvement in leakage volume, the improvement was maintained in the long-term follow-up to 4 years after the treatment (Fig 2). In 5 of 14 patients achieved improvement of leakage volume of more than 50% (Fig.3), with mean leakage volume decreasing from 302.0 g to 84.5 g (72% reduction rate). In the urethral pressure profile, the maximum urethral closing pressure and functional profile length in all patients significantly increased from 35.9 to 45.0 cmH2O and from 16.9 to 24.0 mm (mean), respectively at 6 months after the treatment. Magnetic resonance imaging showed sustained presence of the injected adipose tissue in all patients at 12 months after the treatment. Enhanced ultrasonography showed a progressive increase in blood flow to the injected area up to 12 months after the injection in 13 patients. No significant adverse events were observed peri- or post-operatively.

Interpretation of results

The periurethral injection of ADRCs gradually improved SUI over time in 11 patients. The results of the present clinical trial and a previous experimental study [2] suggest the mechanisms involved in the improvement of the sphincteric function to be bulking effect, regeneration of the smooth muscle, and increased blood flow caused by ADRCs injection. The efficacy of the treatment in improved patients will be durable during a long-term period.

Concluding message

The present study showed that periurethral injection of autologous ADRCs is a safe and feasible treatment modality with durable efficacy for patients with stress urinary incontinence caused by urethral sphincter deficiency. Based on the outcomes of the clinical study, we started a multicentre, investigator initiated clinical trial (ADRESU trial), approved by Japanese PMDA (Pharmaceuticals and Medical Devices Agency) from September 2016 (UMIN-CTR : UMIN 000017901, Clinical Trials. gov : NCT02529865).

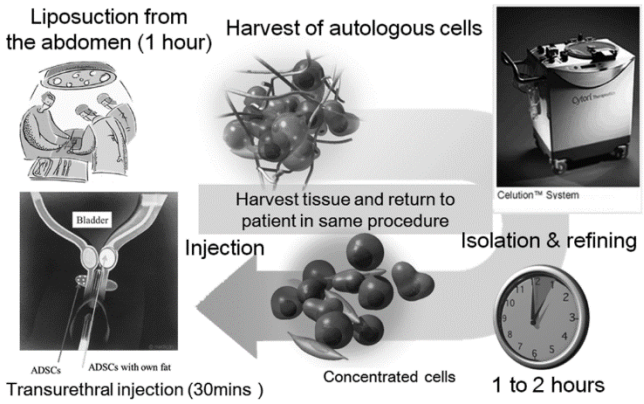

Fig.1: Flow diagram of the periurethral injection of autologous ADRCs

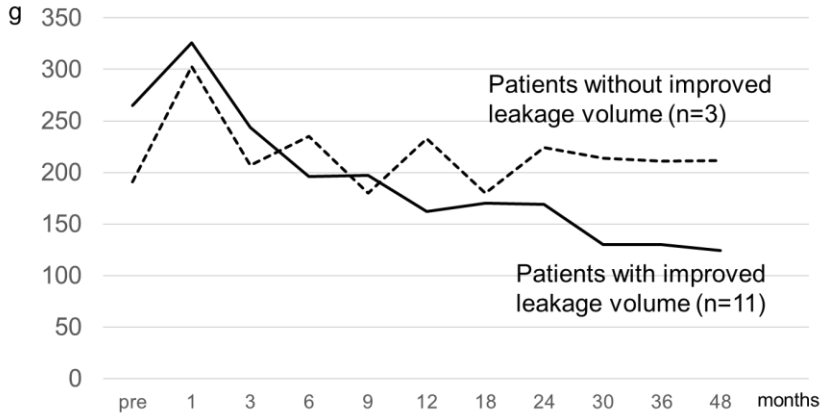

Fig.2: Changes in daily leakage volume in a long-term follow-up

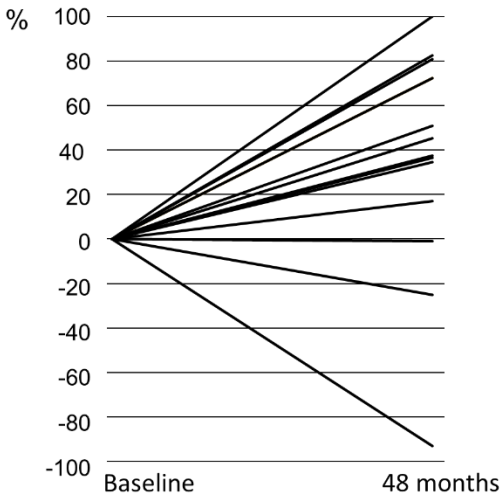

Fig.3: Reduction rates of daily leakage volume in 14 cases

Disclosures
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