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SKELETAL MUSCLE-DERIVED CELL IMPLANTATION IN FEMALE PATIENTS WITH STRESS URINARY INCONTINENCE: A MULTICENTER, RANDOMIZED, PARALLEL-GROUP, PLACEBO-CONTROLLED CLINICAL STUDY

Hypothesis / aims of study

Purpose of this phase IIb study was, to find the optimal dosage for treatment of stress urinary incontinence by implantation of autologous myoblasts into the urethral sphincter and to assess efficacy and safety.

Study design, materials and methods

Between 06/2010 and 06/2011 women, aged 18 to 75 years with proven stress urinary incontinence and an amount of leaked urine of 2 ml up to 50 ml in a one hour pad test were included in the study. Each patient had a history of failed or refused pelvic floor muscle training. Patients with a history of previous anti incontinence surgery were excluded. Urodynamic studies were done prior to randomization to exclude patients with detrusor overactivity. 263 women were randomized, 227 patients were included in the safety set and 217 patients (ITT population) were evaluable for efficacy. Patients were randomized in an open manner to cell implantation or control groups and in a double-blind manner to either high ($10x10^6$) or low ($0.2x10^6$) cell count implantation or to placebo or duloxetine treatment (ratio 2:2:2:1; planned sample size: 60:60:60:30). Duloxetine (max. 80 mg/d) was included in the study to blind the placebo. Patients in the cell implantation arms received a muscle biopsy from the pectoralis or biceps muscle under local anaesthesia. Autologous satellite cells were isolated, brought into culture and expanded up to the desired cell number. Transurethral injection of cells was done under general anaesthesia with a device enabling a standardized ultrasound-directed implantation of cells into the external urethral sphincter with high precision. Afterwards all treatment and control groups performed electrical stimulation of the pelvic floor for 12 weeks.

Table 1: Demographics at baseline (safety set)

	Low cell count	**High cell count**	**Placebo**	**Duloxetine**
	N = 64	N = 56	N = 72	N = 35
Age [years]	54.4 (13.1)	55.2 (11.1)	58.1 (11.7)	61.6 (11.8)
BMI [kg/m²]	26.9 (5.0)	29.3 (6.4)	27.7 (5.9)	27.8 (5.2)
Disease duration [m]	69.9 (65.3)	66.4 (65.6)	63.6 (56.5)	56.3 (52.9)

Values are mean (standard deviation)

Primary efficacy endpoint of the study was the change from baseline in the IEF score 12 weeks after treatment. Therefore patients had to document incontinence episodes in a diary over one week prior to each visit. Secondary endpoints reported here were responder rates based on the percentage of reduction of incontinence episodes, changes in the I-QoL score and the one hour pad test. For safety evaluation all adverse events were analyzed.

Results

For safety evaluation 120 patients treated with cell implantation were evaluated. No patient died during the course of the trial and no treatment related serious adverse events were reported for the cell implantation groups. The most common adverse events with at least possible relation to treatment were urethral or post procedural hemorrhage with a frequency of 7 episodes of mild intensity in both cell groups. Urgency or frequency Symptoms were observed in 3 and urinary tract infections in 2 cases of mild intensity.

The evaluation of the primary efficacy variable revealed a reduction in the mean IEF score in all groups (Table 2). Superiority of cell implantation over placebo was observed for low cell count ($p=0.0019$) as well as high cell count ($p=0.002$). One of the secondary efficacy variables was the change in the pad weight from baseline (Table 2). A decrease in pad weight was observed in all groups but cell implantation showed superiority of the low and high cell implantation groups over placebo treatment ($p=0.0005$, $p<0.0001$ respectively) and duloxetine treatment ($p=0.0051$, $p=0.0023$ respectively)

Table 2: Pre-post comparison 12 weeks after treatment

	Low cell count	High cell count	Placebo	Duloxetine
N (ITT-set)	61	56	68	32
IEF [Episodes/w]				
Pre-treatment mean	25.2	28.6	25.1	26.8
Post-treatment mean	8.8	10.2	16.1	15.4
Difference mean (SD)	-16.4 (13.3)	-18.4 (18.6)	-9.0 (13.1)	-11.4 (18.2)
Pad test [g]				
Pre-treatment mean	15.4	16.0	14.6	17.4
Post-treatment mean	4.5	4.7	8.0	10.5
Difference mean (SD)	-10.9 (9.0)	-11.3 (8.1)	-6.7 (9.4)	-6.8 (11.7)
I-QoI (total scores)				
Pre-treatment mean	43.5	41.7	43.6	42.4
Post-treatment mean	74.8	74.8	58.9	65.6
Difference mean (SD)	31.3 (25.3)	32.3 (21.3)	13.8 (22.1)	20.2 (17.8)

IEF: Incontinence episode frequency

Measures of Quality of life were evaluated with the I-QoL questionnaire (Table 2). The increase in Quality of life observed in the high cell count group was significantly superior vs. placebo and duloxetine ($p<0.0001$, $p=0.0094$ respectively) which was also true for the low cell count group ($p=0.0002$, $p=0.0438$ respectively. In all cases of pre-defined response criteria, the analysis of responder rates showed significant differences clearly in favour of cell implantation (Table 3).

Table 3: Responder rates after 12 weeks, % (n_r)

Definition of response	Low cell count N = 61	High cell count N = 56	Placebo N = 68	Duloxetine N = 32
[50%]	75.4 (46)	80.4 (45)	44.1 (30)	53.1 (17)
[75%]	60.7 (37)	50.0 (28)	26.5 (18)	28.1 (9)
[90%]	42.6 (26)	28.6 (16)	11.8 (8)	18.8 (6)

(n_r) number of responders, Response defined as 50%, 75% or 90% reduction of IEF compared to baseline. Significant superiority was observed for 50% response: Low vs. Placebo $p=0.0003$, Low vs. Dulox. $p=0.0369$, High vs. Placebo $p<0.0001$, High vs. Dulox. $p=0.0141$, 75% response: Low vs. Placebo $p=0.0002$, Low vs. Dulox $p=0.0043$, High vs. Placebo $p=0.009$, 90% response: Low vs. Placebo $p=0.0001$, Low vs. Dulox. $p=0.0235$, High vs. Placebo $p=0.0229$.

Interpretation of results

In this study we evaluated safety and efficacy of implantation of autologous myoblasts into the urethral sphincter in stress urinary incontinent female patients. For this purpose we used two different concentrations of $0.2x10^6$ and $10x10^6$ cells respectively. The equivalence of both cell doses, with regard to efficacy and safety, was confirmed for all primary and secondary parameters. Treatment related adverse events were of mild intensity and easily treated which leads us to the assumption, that cell therapy for stress urinary incontinence is safe. Regarding the reduction of IEF, leakage during pad test and improvement of quality of life we could demonstrate significant superiority vs. placebo for both cell concentrations. For the secondary efficacy criteria we also observed a superiority of cell therapy vs. duloxetine treatment.

Concluding message

Cell therapy with autologous myoblasts for stress urinary incontinence is safe and shows effectiveness after 12 weeks of follow up independently of the dosage used.

Disclosures

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