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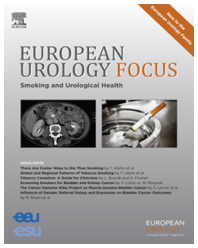

Brief Correspondence

Intracavernous Injections of Bone Marrow Mononucleated Cells for Postradical Prostatectomy Erectile Dysfunction: Final Results of the INSTIN Clinical Trial

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Abstract

We recently reported stage I of a phase 1/2 clinical trial of cell therapy to treat postradical prostatectomy erectile dysfunction (INSTIN, INtra-cavernous STem-cell INjection clinical trial, NCT01089387). In this first stage, four doses of intracavernous autologous bone marrow mononuclear cells (BM-MNCs) were tested in 12 patients. Here, we report the results of stage II, in which six additional patients received the optimal dose identified in stage I (10^9 BM-MNCs), and the long-term results in the 12 patients included in stage I. The objectives were to assess the safety and efficacy of this new treatment. In stage II, no patients had side effects, and the erectile function improvements were similar to those seen in stage I: after 6 months, significant improvements versus baseline were noted in International Index of Erectile Function-15 intercourse satisfaction (7.8 ± 3.1 vs 2.2 ± 3.4, $p = 0.033$) and erectile function (18 ± 8.3 vs 3.7 ± 4.1, $p = 0.035$) domains. In stage I patients, after a mean follow-up of 62.1 ± 11.7 mo, there were no prostate cancer recurrences, and erectile function scores were somewhat lower compared with the 1-yr time point. These findings suggest that intracavernous BM-MNC injections are safe and improve erectile function. The decline in erectile function over time suggests a need for assessing repeated injections.

Patient summary: We report a phase 1/2 pilot clinical trial of cell therapy consisting in intracavernous injection of bone marrow mononuclear cells to treat postradical prostatectomy erectile dysfunction. Erectile function was improved after 6 mo in the patients given 1×10^9 cells. No serious side effects (life threatening or requiring hospitalisation) occurred after a mean follow-up of 62.1 mo in the first 12 patients.

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We recently reported the results of the first stage of a 1-yr, nonrandomised, dose-escalation, phase 1/2, pilot, clinical trial investigating the intracavernous injection of bone marrow mononuclear cells (BM-MNCs) in patients with severe postradical prostatectomy erectile dysfunction (pRP-ED; NCT01089387) [1].

The study design was described previously [1]. Briefly, we included 12 men aged 45–70 yr who had a history of

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radical prostatectomy (RP) within the past 6 mo to 3 yr to treat localised prostatic adenocarcinoma (pT2-N0-M0-R0) followed by pRP-ED with penile arterial insufficiency and/or veno-occlusive dysfunction documented using colour duplex Doppler ultrasound. Other inclusion criteria were failure of pharmacotherapy, defined as an erection hardness score (EHS) of <3 after at least 10 intracavernous alprostadil injections (20 μg) combined with sildenafil (100 mg) and the use of a vacuum device, and erections hard enough to have satisfactory intercourses without the use of erectogenic drugs before RP. The primary objective was to assess the safety of intracavernous BM-MNCs used to treat pRP-ED. The secondary objective was to evaluate the effects of BM-MNC injection on sexual function. Sexual function was evaluated at baseline then at 1, 3, and 6 mo postinjection and at the last follow-up, using both the EHS with and without erectogenic drugs and the International Index of Erectile Function (IIEF-15).

The required sample size was estimated according to Gehan's two-stage design [2] as described previously [1]. At the end of the first stage, the third dose of BM-MNC (10^9 cells) was chosen for the second stage. The number of additional individuals to include depended on the number of "success" (ie, no adverse events) in the first stage. In case of no success, the study was stopped; if one success was observed, 19 additional patients were required; if two successes, six additional patients were required; and if three successes, no additional patients were required. Since no adverse event has been observed during the first stage, the second stage was rapidly stopped after the recruitment of six additional patients.

Here, we report the clinical outcomes of the second stage of the study. In addition, we report the long-term outcomes of the patients included in the first stage.

The mean patient age at baseline was 59.9 ± 3.8 yr in the six stage II patients and 63.9 ± 4.4 yr in stage I patients; mean time from RP to BM-MNC injection was 26.3 ± 6.4 (range 21–36) and 24.4 ± 9.8 mo, respectively. All stage II patients had arterial insufficiency at baseline (mean peak systolic velocity in cavernous arteries after alprostadil injection [20 μg] = 18.4 ± 5.3 cm/s).

No cases of priapism, hematoma, local inflammation, or infectious symptoms were recorded after the BM-MNC injection. At all follow-up visits of all patients, prostate-specific antigen was undetectable and the digital rectal examination showed no evidence of prostate cancer recurrence.

In the six stage II patients, BM-MNC injection significantly improved most of the sexual scores at 6 mo compared with baseline (Table 1), including the IIEF-15 scores for erectile function (+14.4 ± 5, $p = 0.035$), orgasmic function (+4 ± 1.8, $p = 0.034$), overall satisfaction (3.5 ± 2.3, $p = 0.035$), and intercourse satisfaction (+5.6 ± 1.5, $p = 0.033$). At M6, all patients described on-medication erections sufficient for penetration (EHS = 3 or 4) with the use of one erectogenic treatment (sildenafil, $n = 2$; alprostadil, $n = 4$).

Overall, results from stage II of the study showed similar improvements in erectile function compared with those from stage I, after 6 mo (Table 1). Thus, all patients had severe erectile dysfunction at baseline (IIEF-erectile function score <10 with maximal medical treatment), and the

Table 1 – Changes in sexual function scores after intracavernous injection of bone marrow mononuclear cells.

	Baseline[b]	Month 1		Month 3		Month 6		Month 12	Last follow-up	
			p value		*p* value		*p* value			*p* value[c]
Stage I ($n = 9$)[a]										
IIEF-IS	4.6 ± 2	4.9 ± 3.1	0.81	7 ± 4.4	0.078	7.2 ± 3.6	**0.035**	6.9 ± 3.4	6 ± 3.5	0.44
IIEF-SD	6.4 ± 2.7	6.2 ± 2.4	0.87	7.3 ± 1.6	0.23	7.6 ± 1.6	0.16	7.6 ± 1.1	7 ± 1.5	0.85
IIEF-OS	3.9 ± 2.3	2.9 ± 2	0.41	5 ± 3.1	0.36	5.8 ± 2.3	0.15	5.8 ± 2.7	4.4 ± 3.2	0.14
IIEF-EF (with pharmacotherapy)	7.1 ± 3.1	10 ± 9.8	0.64	14.8 ± 10.3	0.092	18.4 ± 8.2	**0.0091**	18.1 ± 7	15.3 ± 8.1	0.22
IIEF-OF	3.8 ± 3.1	4 ± 3.6	0.19	5.9 ± 3.4	0.44	6.3 ± 2.6	**0.024**	6 ± 2.4	5.9 ± 3.8	1
EHS with pharmacotherapy	1.4 ± 0.7	1.4 ± 0.9	1	2.4 ± 1.4	0.11	2.9 ± 0.8	**0.02**	3 ± 0.5	2.5 ± 0.9	0.11
EHS without pharmacotherapy	0.6 ± 0.7	0.8 ± 0.8	0.34	0.9 ± 1.3	0.37	1.2 ± 1.2	0.09	1.6 ± 1.3	1.3 ± 1	0.5
Stage II ($n = 6$)										
IIEF-IS	2.2 ± 3.4	5.7 ± 4.5	**0.058**	8.5 ± 3.6	**0.031**	7.8 ± 3.1	**0.033**	–	–	–
IIEF-SD	6.2 ± 1.8	6.2 ± 2.3	**0.058**	7 ± 0.9	0.17	6.7 ± 1	0.34	–	–	–
IIEF-OS	3.3 ± 2.4	3.5 ± 2	0.88	5.5 ± 2.9	0.41	6.8 ± 2.5	**0.035**	–	–	–
IIEF-EF (with pharmacotherapy)	3.7 ± 4.1	11.8 ± 11.6	0.062	18.2 ± 10.3	**0.031**	18 ± 8.3	**0.035**	–	–	–
IIEF-OF	3.3 ± 3.2	6 ± 3.1	0.073	8.2 ± 2.9	0.062	7.3 ± 2.3	**0.034**	–	–	–
EHS with pharmacotherapy	1.8 ± 0.8	2.2 ± 1.5	0.85	2.7 ± 1.2	0.41	3.3 ± 0.8	**0.053**	–	–	–
EHS without pharmacotherapy	0.8 ± 0.8	1.5 ± 1	0.46	1.3 ± 1	0.5	1.2 ± 0.4	0.58	–	–	–

IIEF = International Index of Erectile Function.
Sexual function with pharmacotherapy was assessed based on IIEF-15 questionnaire subscores for intercourse satisfaction (IS), sexual drive (SD), overall satisfaction (OS), erectile function (EF), and orgasmic function (OF), and on the erection hardness score (EHS). Spontaneous erections were evaluated by asking patients to determine their EHS without pharmacotherapy. The data are mean ± standard deviation. Significant differences compared with baseline are in bold type.
[a] Data are reported only for the nine patients of stage I who did not receive a penile implant at the last follow-up (62.1 ± 11.7 mo).
[b] Baseline scores were reported when using the maximal medical treatment associating sildenafil 100 mg + alprostadil 20 μg and the use of a vacuum device.
[c] Values at last follow-up (62.1 ± 11.7 mo) were compared with those after 12 mo.

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mean IIEF-erectile function score was 18 after 6 mo, suggesting that BM-MNC injection may improve the response to medical treatment.

Among the 12 stage I patients, three subsequently asked for penile prosthesis (after 2 yr), because they felt that the medical treatment was unduly burdensome. However, these patients had an EHS score of 3 ($n = 2$) or 4 ($n = 1$) (allowing penetration) using alprostadil injections ($n = 2$) or vacuum therapy alone ($n = 1$). No technical difficulties arose during prosthesis implantation. Table 1 shows the sexual scores in the remaining nine patients included in stage I after a mean follow-up of 62.1 ± 11.7 mo. There was a nonsignificant decline in the IIEF-erectile function at the last follow-up, compared with the 1-yr time point (15.3 ± 8.1 vs 18.1 ± 7).

Overall, our results suggest that intracavernous BM-MNC injection may be safe and may benefit erectile function in patients with severe erectile dysfunction refractory to medical treatment. Given the lack of control group, we cannot eliminate the hypothesis of a spontaneous recovery in our study. It has been shown that erectile function may improve up to 4 yr after RP [3,4]; however, the kinetics and magnitude of improvement observed in our study (a gain of >10 points in the IIEF-erectile function score within 6 mo after a mean delay of 26.3 mo after RP) clearly do not correspond to the profile of natural evolution of erectile function after RP [3,4]. In addition, the refractoriness to medical treatment is considered a sign of end-stage disease requiring penile prosthesis implantation [5–7].

Importantly, no evidence of prostate cancer recurrence was observed after BM-MNC injection in the first 12 patients after a mean follow-up of 5 yr. Reactivation of cancer cells by cell therapy is of concern [8]. We therefore confined our study to patients with localised prostate cancer to minimise this risk.

The erectile function improvements tended to decrease over time in stage I patients. Whether this finding reflects the normal age-related decrease in erectile function or loss of efficacy of BM-MNC injection is unclear. Our results raise the possibility that repeat injections may be needed to optimise or maintain the treatment effects.

Further controlled studies are required to further elucidate the effects of this new therapeutic strategy and assess the determining factors of success.

Author contributions: René Yiou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Yiou, Rouard.
Acquisition of data: Hamidou, Birebent, Bitari.
Analysis and interpretation of data: Yiou, Rouard, Roudot-Thoraval.
Drafting of the manuscript: Yiou, Rouard.
Critical revision of the manuscript for important intellectual content: de la Taille, Rodriguez.
Statistical analysis: Roudot-Thoraval.
Obtaining funding: Yiou, Rouard.
Administrative, technical, or material support: Le Corvoisier, Contremoulins, Augustin.
Supervision: Yiou.
Other: None.

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