A drug-coated balloon treatment for urethral stricture disease: Interim results from the ROBUST I study

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Abstract

Introduction: We aimed to investigate the safety and preliminary efficacy of the Optilume™ paclitaxel-coated balloon for the treatment of recurrent urethral stricture.

Methods: Men with bulbar urethral strictures ≤2 cm with 1–4 prior endoscopic treatments were enrolled at four study sites after ethics committee approvals. All subjects were treated with mechanical balloon dilation or direct visualization internal urethrotomy prior to drug-coated balloon treatment. Patients were evaluated at 2–5 days, 14 days, three, six, and 12-months post-treatment. The primary safety endpoint was serious complications through 90 days post-procedure. The preliminary efficacy endpoint was anatomic success, defined as urethral lumen ≥14 Fr at 12 months.

Results: A total of 53 subjects were enrolled and treated; 46 completed the 12-month followup. Forty-three percent of men had undergone >1 previous dilation; the mean for the overall study population was 1.7 prior dilations. There were no serious adverse events related to the treatment within 90 days. Anatomic success was achieved in 32/46 (70%; 95% confidence interval [CI] 54–82%) at 12 months. The 14 failures included seven cystoscopic recurrences, five retreatments, and two patients who exited the study early due to symptom recurrence.

Conclusions: One-year data indicates the Optilume paclitaxel-coated balloon is safe for the treatment of recurrent bulbar urethral strictures. Early efficacy results are encouraging and support further followup of these men through five years, as well as further investigation with a randomized trial.

Introduction

Approximately 0.6% of men experience a urethral stricture in their lifetime.[1] Treatment options include dilation (rigid or balloon), direct visual internal urethrotomy (DVIU), implanted stent, and urethroplasty. Dilation and DVIU comprise 95% of urethral stricture treatments, as they are minimally invasive, low-cost, and can be performed by any urologist; but recurrence rates are high.[2] A recent review demonstrated a 90% lifetime recurrence rate, even for first-time dilations, and near 100% for repeat dilations.[3] Dilation and DVIU have similar outcomes, whereas urethroplasty has the highest rate of success.[4-7] Steroid or mitomycin C (MMC) injection have been used as an adjuvant to endoscopic treatment, but results have been mixed.[8-11]

The Optilume™ drug-coated balloon (DCB; Urotronic, Plymouth, MN) combines dilation with circumferential delivery of paclitaxel. Paclitaxel is an anti-fibrotic, anti-proliferative drug that is used as a coating in minimally invasive vascular applications to prevent restenosis.[12-14] ROBUST I is a prospective study evaluating the safety and preliminary efficacy of DCB for urethral stricture.

Methods

Study design and participants

This was a single-arm, prospective, open-label study, conducted under a common protocol at four Latin American centers. Eligible patients were men ≥18 years, with a single bulbar urethral stricture <12 Fr and ≤2.0 cm long on urethrogram. Patients were included if they had undergone 1–4 prior endoscopic treatments (none within three months prior to enrollment), had an International Prostate Symptom Score (IPSS) ≥13, and maximum flow rate (Qmax) <10 ml/sec. Patients were excluded for prior urethroplasty, radical prostatectomy, lichen sclerosus, penile prosthesis or artificial urinary sphincter, pelvic radiation, urinary stone passage in previous six months, chronic kidney disease or serum creatinine >2 mg/dL, intradetrusor onabotulinum toxin A injection within 12 months of study entry, neurogenic bladder, bladder or prostate cancer in previous five years, or active non-genitourinary cancer.

Procedures

After a baseline urethrogram, strictures were pre-treated with an uncoated balloon and/or DVIU until lumen diameter increased

by 50%. Although the DCB is intended to be used without pretreatment, we performed pretreatment in this first-in-man study to: 1) ensure the DCB could cross the stricture without disrupting the drug coating; and 2) prevent double dosing patients with a lumen <20 Fr after the first DCB treatment. The DCB was inflated to the rated burst pressure and held for ≥5 minutes. The DCB was 3 cm in length and 24 F (other sizes are now available). Followup was at five 14, 90, 180, and 365 days; annual followup is planned for five years. IPSS was assigned before intervention and at each followup visit. Cystoscopy was performed at 180- and 365-days post-procedure. Due to the variety in size of cystoscopes used (15–20 F), if the cystoscope could not be passed beyond the narrowing but a 14 Fr catheter could be passed atraumatically, this was considered an anatomic success.

Primary safety endpoint

The primary safety endpoint was the rate of treatment-related urinary severe adverse events (SAEs), defined as urethral fistula formation, de novo urinary retention >14 days post-treatment, de novo stress incontinence (>1 pad/day) at 90 days post-treatment, or urethral rupture.

Efficacy endpoint

The efficacy endpoint was defined as one-year anatomic success without retreatment, regardless of symptoms or flow rate. Failure was defined as anatomic failure or retreatment; additionally, any subject who exited the study prior to cystoscopic evaluation with IPSS ≥11 was considered a failure. Subjects were right-censored when lost to followup if IPSS was <11 at exit, or IPSS was ≥11 without recurrence on cystoscopy.

Secondary endpoints

Secondary endpoints included: 1) IPSS; 2) sexual function, using the "overall satisfaction" question of the International Index of Erectile Function (IIEF);[15] 3) Qmax; 4) post-void residual urine volume (PVR); 5) concentration of paclitaxel in the blood, urine, and semen; and 6) pain (Visual Analog Scale, VAS).[16]

Data analysis

Baseline characteristics and the primary safety endpoint were tabulated using descriptive analysis. The number and percentage of subjects experiencing at least one device-related SAE were presented for this endpoint, along with the 95% confidence interval (CI). The preliminary efficacy endpoint was met if the lower limit of the one-sided 95% CI for anatomic success exceeded the reference success rate. The reference rate was drawn from the Steenkamp and Heyns randomized trial of DVIU vs. dilation.[4] This reference success rate varies with the number of prior treatments: 65% at one year for men with 0–1 prior endoscopic procedures and 10% for men with two prior endoscopic procedures.[4] It was unclear a priori how many prior dilations our cohort would have (inclusion criteria were 1–3 prior endoscopic procedures), so we targeted enrollment based on a power calculation using the more stringent 65% success rate.

Results

Patients

Between November 29, 2016 and September 9, 2017, 53 patients were enrolled and treated with the DCB. Average age was 50.7 years (range 22–81) and the majority (83%) were Hispanic/Latino (Table 1). Stricture etiology was traumatic (51%), iatrogenic (45%), or idiopathic (4%). All strictures were bulbar, with an average length of 0.9 cm. Mean stricture narrowing was <9 F and the mean number of endoscopic procedures prior to enrollment was 1.7. Some patients performed intermittent dilation independently, but only the physician-administered procedures were recorded. Seven patients (13.2%) had a suprapubic catheter at the time of enrollment. Pretreatment immedi-

Table 1. Patient demographics and urological medical history (n=53)

Patient demographics	
Age (years)	
Mean ± SD	50.7±15.47
Range	22.0–81.0
Median	50.0
Male gender, n (%)	53 (100.0 %)
Race of subjects, n (%)	
Black or African	8 (15.1 %)
Hispanic or Latino	44 (83.0 %)
Other	1 (1.9 %)
Suprapubic catheter at baseline	7 (13.2 %)
Stricture etiology, n (%)	
Iatrogenic	24 (45.3%)
Idiopathic	2 (3.8%)
Traumatic	27 (50.9%)
Stricture measurements, mean ± SD	
Stricture length (mm)	9.00±5.20
Urethral diameter at stricture (mm)	2.47±1.97
Urethral diameter at area healthy tissue (mm)	10.2±3.62
Pretreatment	
Uncoated balloon	31 (59%)
DVIU	8 (15%)
Uncoated balloon + DVIU	14 (26%)
Number of previous endoscopic treatments, n (%)	
1	30 (57%)
2	13 (25%)
3	8 (15%)
4	2 (4%)

DVIU: direct visual internal urethrotomy; SD: standard deviation.

ately prior to DCB was accomplished with an uncoated balloon in 59%, DVIU in 15%, or uncoated balloon and DVIU in 26%.

Primary safety and preliminary efficacy endpoints

There were no treatment-related urinary SAEs at 90 days post-procedure. There were two SAEs, myocardial infarction and abdominal pain, at six months and 12 months post-procedure, respectively, but unrelated to the procedure. In total, there were 52 adverse events, most commonly urinary tract infection (15%), fever (12%), acute urinary retention (8%), headache (8%), and dysuria (6%). The majority were classified as mild (58%) or moderate (38%) according to the Common Terminology Criteria for Adverse Events, and 25% were categorized as "possibly," "probably," or "definitely" related to the procedure (Fig. 1).

Anatomic success was achieved in 32/46 (70%; 95% CI 54–82%) at 12 months (Table 2). The 14 failures included seven cystoscopic recurrences (six at six months, one at 12 months), five retreatments (four at three months, one at 12 months), and two who exited the study with IPSS >11 prior to cystoscopy (both at three months). Of the six men with cystoscopic recurrence at six months, one underwent retreatment, one exited the study, and four were observed. IPSS in those who were observed remained ≤11 at both six and 12 months. Anatomic success rates did not vary significantly based on the number of prior endoscopic treatments: 77% (23/30) among men with one prior treatment, 62% (8/13) with two treatments, 87% (7/8) with three treatments, and 50% (1/2) in men with four previous treatments (p=0.47). Neither did success rates vary by stricture etiology: 67% (18/27) in traumatic strictures, 83% (20/24) in iatrogenic strictures, and 50% (1/2) in idiopathic strictures (p=0.30).

Table 2. Anatomical success rates over time

Outcomes	Time (months)			
	0	3	6	12
Success	53	45	39	32
Fail – cumulative	0	6	12	14
Censor – cumulative	0	2	2	7
Number remaining for analysis (total – censor)	53	51	51	46
Success (%)	100	88	76	70

Failure defined as inability to pass a cystoscope and a 14 Fr catheter (n=7), retreatment (n=5), exit with International Prostate Symptom Score (IPSS) >11 but no cystoscopy performed (n=2). Success defined as normal cystoscopy or 14 Fr catheter test without retreatment, regardless of symptoms (symptoms without stricture is presumed to be benign prostatic hyperplasia). Censor: exit/lost to followup without symptoms and normal cystoscopy or 14 Fr catheter test.

Secondary endpoints

Baseline IPSS ranged from 15–34 with a mean of 25.2 (±4.5), and IPSS quality of life (QOL) ranged from 2–6 with a mean of 4.9 (±0.9). At 90 days post-procedure, mean IPSS and IPSS-QOL were 6.1 (±7.6) and 0.8 (±1.3), respectively. At one year, there was a statistically significant improvement in mean IPSS (4.9±5.6) and IPSS-QOL (0.8±1.1) compared to baseline (p<0.001) (Table 3). Urinary symptom resolution, represented by IPSS <11 without retreatment, occurred in 79% (38/48) at one year. Of note, although the retreatment outcome was definitive, urinary symptoms fluctuated; there were seven men who had IPSS ≥11 at three or six months who then had IPSS <11 at one year without retreatment. Mean IIEF satisfaction scores were 6.5 (±2.6) at baseline and 7.8 (±2.6) one-year post-treatment (Table 3). Mean Qmax improved from 5.0 ml/sec (baseline) to 23.6, 24.2, 22.2, 20.5, and 19.5 ml/sec at the 14-, 30-, 90-, 180-, and 365-day followups. Additionally, the average PVR decreased from 141.0 ml (baseline) to 27.3 ml and 26.7 ml at the 180- and 365-day followups, respectively (Table 3).

Urinary paclitaxel concentration was 184.3±179.1 ng/ml immediately post-procedure (n=52) and 2.6±4.8 ng/mL at five days (n=21). Plasma paclitaxel concentration was very low, as it was near the limit of quantification immediately post-procedure (low=0.1 ng/mL). Semen paclitaxel concentration was low: 2.5±2.9 ng/mL (n=31) at 14 days and

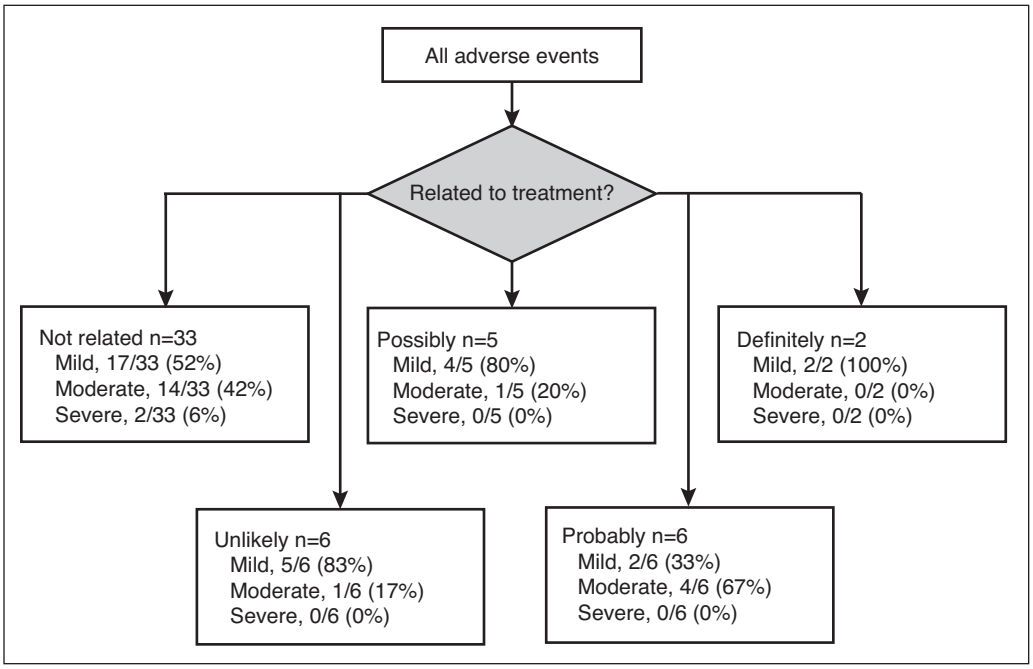

Fig. 1. Adverse event, relation to treatment, and severity. Severity was determined using the Common Terminology Criteria for Adverse Events (CTCAE v4.0) severity scale.

Table 3. Results of secondary endpoints

Category	Baseline	14 days	30 days	90 days	180 days	365 days
IPSS score						
Mean ± SD	25.2±4.46	5.1±5.45	4.3±5.95	6.1±7.63	4.8±6.41	a4.9±5.63
n	53	51	51	51	47	42
Range	15.0–34.0	0.0–33.0	0.0–34.0	0.0–30.0	0.0–34.0	0.0–31.0
Median	26.0	4.0	2.0	3.0	3.0	3.5
IPSS QOL						
Mean ± SD	4.9±0.86	0.8±0.94	0.7±1.05	0.8±1.32	0.7±1.02	0.8±1.06[a]
n	53	51	51	51	47	42
Range	2.0–6.0	0.0–5.0	0.0–6.0	0.0–5.0	0.0–4.0	0.0–4.0
Median	5.0	1.0	0.0	0.0	0.0	0.0
IIEF: Overall satisfaction						
Mean ±S D	6.5±2.62	[b]	7.1±2.49 51	7.9±2.53 51	7.6±2.82 47	7.8±2.62 42
n	53		2.0–10.0	2.0–10.0	2.0–10.0	2.0–10.0
Range	2.0–10.0		8.0	8.0	8.0	8.5
Median	6.0					
Qmax (mL/sec)						
Mean ± SD	5.0±2.56	23.6±12.63	24.2±14.15	22.2±12.49	20.5±10.36	a19.5±9.96
n	46	51	50	51	47	42
Range	0.0–10.0	5.0–52.0	5.9–67.3	2.0–50.0	3.0–50.0	4.9–40.5
Median	5.0	21.3	20.5	19.6	19.0	18.0
PVR (mL)						
Mean ± SD	141.4±105.05	32.7±33.06	33.0±33.51	36.1±36.24	27.3±41.68	[a]26.79±33.10
n	43	49	49	51	47	42
Range	0.0–462.0	0.0–132.0	0.0–181.9	0.0–150.0	0.0–200.0	0.0–163.0
Median	128.0	24.0	25.0	26.0	13.0	19.0
VAS pain score						
Mean ± SD	2.9±2.87	0.6±0.98	0.9±1.87	0.9±1.87	0.9±1.87	0.9±1.87
n	53	51	51	51	51	51
Range	0.0–10.0	0.0 –4.0	0.0 –8.0	0.0 –8.0	0.0 –8.0	0.0 –8.0
Median	3.0	0.0	0.0	0.0	0.0	0.0

[a]Comparing to the baseline value, p<0.001. [b]The patients were asked to refrain from sexual intercourse until day 30; therefore, the relevant comparison of IIEF scores is at baseline, 30 days, and beyond.
IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; SD: standard deviation; PVR: post-void residual; Qmax: maximum urinary flow rate; QOL: quality of life; VAS: Visual Analog Scale.

1.0±1.6 ng/mL (n=24) at 30 days post-procedure. Most patients experienced only minor pre-procedure pain associated with their stricture disease, with a mean VAS score of 2.9 (±2.87). Mean VAS scores decreased to 0.6 (±1.0) and 0.9 (±1.9) at 14 and 30 days (Table 3).

Discussion

The ROBUST I trial is a multicenter, single-arm, open-label study investigating the safety and efficacy of the Optilume DCB among male patients with a single bulbar recurrent urethral stricture. There were no treatment-related SAEs. Most side effects were mild or moderate in severity; the most common was urinary tract infection. When paclitaxel is used for chemotherapy, drug-related side effects include neurotoxicity and myelosuppression;[17] these were not seen in the current study. Paclitaxel urine concentrations immediately post-procedure were about six times lower than in chemotherapy patients and dropped significantly by five days; serum levels were also very low.[18]

This study will eventually yield five-year efficacy outcomes; herein, we report preliminary one-year success of 70%, with a 95% CI of 54–82%. The 95% CI did not exceed the reference 65% success rate for men with 0–1 prior dilations in the Steenkamp and Heyns study, but did exceed the reference 10% rate for men with two prior dilations.[3]

Secondary outcome measures demonstrated an improvement in urinary symptoms, urinary quality of life, pain scores, and uroflowmetry, specifically Qmax and PVR. Sexual function was not significantly affected by DCB.

Although this is the first study conducted using a paclitaxel-DCB for urethral strictures, several other studies have investigated other drugs in conjunction with mechanical dilation. A recent study demonstrated 75% patency at two years following DVIU with MMC injection and self-dilation;[19] however, significant adverse effects have been reported after MMC injection into urinary mucosa, including osteitis pubis, urethral fistula formation, and tissue necrosis.[11] Outcomes with urethral triamcinolone as an adjuvant vary widely between studies.[20,21] The Optilume DCB may offer advantages compared to these other adjuvants. First, as a hydrophobic drug it absorbs easily into the target tissue avoiding immediate washout. Second, the half-life of paclitaxel is measured in days whereas the half-life of MMC is hours. This allows paclitaxel to be present during the inflammatory, proliferation, and remodeling stages of wound

healing. Third, the paclitaxel dosing is tightly controlled by the proprietary DCB coating process, avoiding the risks of overdosing with manual injection; in a good laboratory practice animal study acquired prior to study initiation, urethral tissue concentration of paclitaxel drops 73% after seven days and remains quantifiable in most subjects through 28 days. Fourth, paclitaxel is circumferentially delivered topically to the urothelium, reducing the risk of periurethral dosing that can occur with deep injections.

Among the limitations, there was no control arm in this early-phase study. Further, we excluded penile strictures, bladder neck contractures, patients with previous pelvic radiotherapy, and patients with a history of lichen sclerosus; the DCB may perform worse in these strictures, which are known to have a higher risk of recurrence. Furthermore, the 12-month followup does not capture patients with delayed stricture recurrence; however, data suggests the mean time from endoscopic treatment to stricture recurrence is 6–-12 months.[22] We will report five-year results as they become available. There were patients in our cohort who performed self-dilation, but only physician-administered dilations were recorded; it is unknown how this affected stricture recurrence. Future results without pretreatment may differ from those seen in this study, where all patients were pretreated with DIVU or dilation.

Conclusions

The Optilume DCB is safe; early efficacy results are encouraging and support further followup of these men through five years, as well as further investigation with a randomized trial.

Competing interests: Dr. Elliott, Dr. Virasoro, and Dr. DeLong serve as consultants for Urotronic. The remaining authors report no competing personal or financial interests related to this work.

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