

CASE REPORT

Novel Therapy with Intravesical Liposomes for Ulcerative Interstitial Cystitis/Painful Bladder Syndrome

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Objectives: A Federal Drug Administration-approved, compassionate-use, investigational new drug single-subject trial was conducted to evaluate the safety and clinical outcomes of intravesical instillation of liposomes in a woman with ulcerative interstitial cystitis/painful bladder syndrome (IC/PBS).

Methods: After obtaining informed consent, the 48-year-old woman, diagnosed with ulcerative IC/PBS, received four weekly instillations of intravesical liposomes. Subsequently she was evaluated for 8 weeks post bladder instillation.

Results: No side effects or adverse events were reported during the 12 week study period. Voids per day decreased from a baseline of 18 voids per 24 h to 11.3 voids per 24 h at week 3, and 12.6 voids per 24 h at 8 weeks after final instillation. Urgency score also decreased from a pre-instillation mean of 1.75 (out of 10) to 1.07 8 weeks after the final instillation. Bladder ulcers noted by cystoscopy at baseline were absent at the 8 weeks post-treatment and no evidence of bladder inflammation was noted.

Conclusion: Intravesical liposome instillation is minimally invasive and presents an appealing new treatment for IC/PBS. Prospective trials are needed to assess intravesical liposomes for IC/PBS.

Key words interstitial cystitis, intravesical instillation, liposomes, urinary bladder

1. INTRODUCTION

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a poorly understood condition with significant unmet medical needs. Liposomes are vesicles composed of phospholipid bilayers separated by aqueous compartments. They can fuse with cells to provide a molecular film that can promote wound healing. Liposomes are currently used as vehicles for systemic drug delivery in humans, and topical applications in the vagina and cul-de-sac of the eye.^{1–5} LP-08 (Lipella Pharmaceuticals, Inc., Pittsburgh, PA, USA) are therapeutic “empty” liposomes developed for the intravesical treatment of IC. The specific aims of the study were to determine the safety and clinical outcomes of four weekly bladder instillations of therapeutic liposome.

2. CASE REPORT

The study subject was first diagnosed with ulcerative IC/PBS in 2003. Her symptoms included persistent urinary urgency, frequency and pelvic pain. Past treatments included Oxybutynin, Pentosan, Valdecoxib, Hydroxyzine, Phenazopyridine, and Mycophenolate without adequate relief. Patient reported temporary improvements with hydrodistention and cautery of ulcers. Maximum bladder capacity was 425 cc, with terminal hematuria and multiple glomerulations found throughout the bladder.

After obtaining Investigational Review Board approval and obtaining written informed consent, the subject underwent a single course of treatment consisting of four weekly instillations of 80 mg LP-08 in 40 cc of distilled water. For each instillation, a solution of LP-08 was prepared and instilled into the empty bladder via 8 Fr catheter with 2% lidocaine jelly applied to the catheter tip prior to insertion.

For a 12-week period, the subject's general health, urinary function and symptoms were monitored and evaluated. Primary efficacy measurements of health-related quality of life included voiding diary, global response assessments, and O'Leary Sant Interstitial Cystitis Symptom and Problem Indices (ICSI and ICPI).⁶ Voiding diaries were completed to assess urinary frequency, urgency, leaking and pelvic and/or bladder related pain.

Subject indicated urinary frequency decreased from a baseline mean of 18 episodes/24 h pretreatment to a mean

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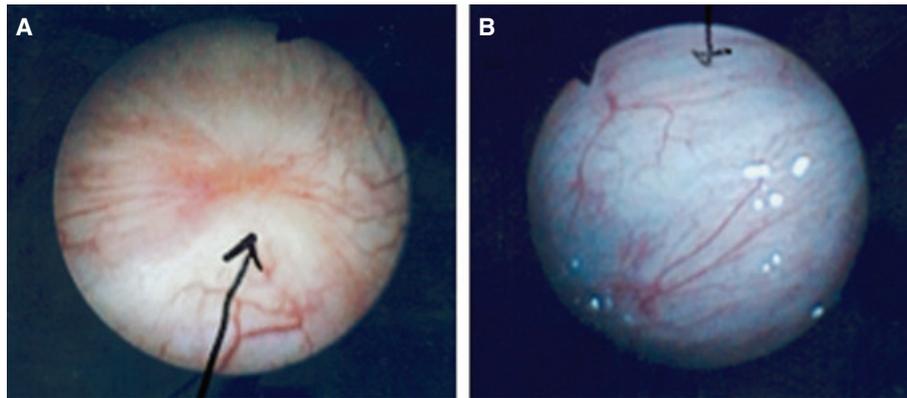


Fig. 1 (a) Pre-treatment. (b) Eight weeks post intravesical liposome instillation illustrating ulcer resolution. Arrows indicate bladder ulcer.

of 11.3 episodes/24 h at 3 weeks, and 12.6 episodes/24 h 8 weeks after the first instillation. The urgency score also decreased from a pre-instillation mean score of 1.75 (out of 10) to a mean score of 1.07 8 weeks after the final instillation. A comparison of cystoscopy findings at the time of the initial instillation and 8 weeks post-treatment revealed a marked improvement in bladder appearance (Fig. 1). Three bladder ulcers noted at baseline were absent at 8 weeks post-treatment. No evidence of bladder inflammation was noted 8 weeks after final instillation and the erythema was also markedly improved. Responses to both the ICSI and ICPI fell notably over the course of treatment. Subject responses on the global response assessments indicated a slight improvement across the duration of treatment. The patient, currently in clinic follow-up, reported the treatment benefit lasting over 6 months.

No adverse events or treatment-related side effects were reported by the study subject at any time throughout the course of the study. The study subject denied gross hematuria, urinary retention, urgency, frequency and signs/symptoms of infection (i.e. odor, cloudiness and dysuria). She denied bladder irritation after instillation and she was able to void without difficulty. Pelvic and bladder pain were also routinely assessed at multiple time points during each treatment visit. Overall, the subject reported pain scores ranging from 0 to 2, on a scale from 0 (none) to 10 ("the worst pain you've ever experienced"). Antiphospholipid Antibody Panel results were negative pre- and post-treatment.

3. DISCUSSION

Pre-clinical efficacy of intravesical liposomes was compared against the instillation of dimethyl sulfoxide and Elmiron (Ortho-McNeil-Janssen Pharmaceuticals, Inc., Titusville, NJ, USA) in a bladder injury model induced by protamine sulfate/potassium chloride. Dimethyl sulfoxide is used as a 50% solution to treat IC/PBS patients.⁷ Elmiron (pentosan polysulfate) 6 mg/mL (the concentration in saline solution typically employed in the clinic off-label for intravesical administration) was evaluated.⁸ Intravesical liposomes induced the greatest increase in

the intercontractile interval, the surrogate measurement of efficacy. Histological studies also indicate that intravesical liposomes act as a protective urothelial coating.^{9,10} Plasma analysis of LP-08-treated rats concluded that there is no systemic exposure to sphingomyelin or metabolites, either acute or chronic. Chuang et al.,¹¹ recently published their results of physician initiated intravesical liposomes versus oral pentosan polysulfate in 24 IC/PBS patients (12 in each group). In the clinic, LP-08 (80 mg LP-08/40 cc distilled water) was instilled into the bladder using an 8 French catheter with 2% lidocaine jelly applied to the tip. LPs were retained for 30–60 min. In this study there were no unanticipated adverse events, worsening of symptoms, or urinary incontinence, retention, or infection after instillation of LP-08 into the bladder. Only two patients in the LP group had mild pain while holding LP in the bladder for up to 60 min. Our study extended the report by Chuang et al.,¹¹ with LP-08 able to aid ulcerative IC/PBS.

Statistically significant decreases in urinary frequency, nocturia, pain, urgency, and validated symptom scores were noted at 4 and 8 weeks after instillation. At week 8, three patients also had decreased bladder inflammation noted on cystoscopy. Outcomes from the current study also indicated symptom improvements across the multiple domains tested. Subject outcomes were favorable with no side effects or adverse events occurring during treatment and throughout the 8 weeks of follow-up care.

In conclusion, intravesical liposomal instillation was safe and beneficial in a patient with refractory IC/PBS. Further trials are needed to fully explore this new treatment modality.

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Disclosure

Kenneth Peters, Deborah Hasenau, and Kim Killinger do not have any information to disclose. Jonathan Kaufman and Michele Anthony are employees of Lipella Pharmaceuticals, Inc.

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