Pentosan Polysulfate Sodium for Treatment of Interstitial Cystitis/Bladder Pain Syndrome: Insights from a Randomized, Double-Blind, Placebo Controlled Study

J. Curtis Nickel,*,† Sender Herschorn,‡ Kristene E. Whitmore,§ John B. Forrest,‖ Peter Hu,¶ Andrew J. Friedman¶ and Alan S. Baseman¶

From the Queen's University, Kingston General Hospital (JCN), Kingston and Sunnybrook Health Sciences Centre (SH), Toronto, Ontario, Canada, Drexel University College of Medicine (KEW), Philadelphia, Pennsylvania, Urologic Specialists of Oklahoma, Inc. (JBF), Tulsa, Oklahoma, and Janssen Research & Development, L.L.C. (PH, AJF, ASB), Raritan/Titusville, New Jersey

Purpose: We compared the efficacy and safety of the currently recommended dose of pentosan polysulfate sodium with a third of the daily dose and with placebo.

Materials and Methods: In this multicenter, double-blind, randomized, placebo controlled study 368 adults with interstitial cystitis/bladder pain syndrome, defined as an ICSI total score of 8 or greater and a score of greater than 0 on the 4 ICSI component items, received pentosan polysulfate sodium 100 mg once daily or 3 times daily, or matching placebo for 24 weeks. Study eligibility was not based on cystoscopy findings. ICSI was administered at baseline, and at weeks 4, 8, 12, 18 and 24. Unblinded interim analysis performed at 6 years with 54% of the target number of 645 patients enrolled resulted in early study termination.

Results: There was no statistically significant difference between the pentosan polysulfate sodium group and the placebo group or between the 2 pentosan polysulfate sodium groups for the primary end point, defined as responder achieving a 30% or greater reduction from the baseline ICSI total score at study end. This primary end point was achieved by 48 of 118 patients (40.7%) in the placebo group, and by 51 of 128 (39.8%) and 52 of 122 (42.6%) in the pentosan polysulfate sodium 100 mg once daily and 3 times daily groups, respectively. Pentosan polysulfate sodium was well tolerated with a similar percent of patients (range 10.2% to 13.3%) across the groups discontinuing due to an adverse event.

Conclusions: Results of this study in a broad population of patients with symptoms consistent with interstitial cystitis revealed no treatment effect vs placebo for pentosan polysulfate sodium at the currently established dose or at a third of the daily dose.

Abbreviations and Acronyms

BPS = bladder pain syndrome

FDA = Food and Drug Administration

GRA = global response assessment

IA = interim analysis

IC = interstitial cystitis

ICSI = O'Leary-Sant Interstitial Cystitis Symptom Index

ITT = intent to treat

NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases

PORIS = Patient's Overall Rating of Improvement of Symptoms

PPS = pentosan polysulfate sodium

QD = once daily

TID = 3 times daily

Accepted for publication September 10, 2014.

Study received independent review or research ethics board approval at each participating hospital.

Supported by Janssen Research & Development.

* Correspondence and requests for reprints: Department of Urology, Queen's University, Kingston General Hospital, Kingston, Ontario, Canada, K7L 2V7 (telephone: 613-548-2497; FAX: 613-545-1970; e-mail: jcn@queensu.ca).

† Financial interest and/or other relationship with GlaxoSmithKline, Taris Biomedical, Pfizer, Eli Lilly, Johnson & Johnson, Farr Labs, Astellas, Trillium Therapeutics, Auxilium, Ferring and Tribute.

‡ Financial interest and/or other relationship with Johnson & Johnson.

§ Financial interest and/or other relationship with Coloplast, Pfizer, Neocutis and MedTronics.

‖ Financial interest and/or other relationship with Urologic Specialists of Oklahoma.

¶ Financial interest and/or other relationship with Janssen Research & Development.

0022-5347/15/1933-0857/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.09.036
Vol. 193, 857-862, March 2015
Printed in U.S.A.

Key Words: urinary bladder; cystitis, interstitial; pentosan sulfuric polyester; treatment outcome; questionnaires

Interstitial cystitis, recently referred to as IC/BPS, is characterized by "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptom(s) of more than 6 weeks duration, in the absence of infection or other identifiable causes."[1] Consensus is lacking on the pathophysiology, etiology and classification of IC/BPS, resulting in diagnoses made by clinical exclusion rather than by objective measures. The population of patients with an IC/BPS diagnosis comprises multiple clinical phenotypes,[2,3] likely from diverse combinations of etiologies, symptom complexes, progression trajectories and associated comorbidities. A specific phenotype is related to traditional IC as defined in 1988 by the NIDDK.[4] This includes rigid criteria related to urinary symptoms, of which the most critical are urinary urgency and bladder pain,[5] as well as objective cystoscopic and urodynamic parameters. While the approach to IC/BPS treatment varies widely in clinical practice, there is general accord for some agents, notably amitriptyline, hydroxyzine and PPS.[1,6]

Oral PPS is approved in the United States for relief of the bladder pain or discomfort associated with IC and in Canada for initial and maintenance treatment of IC. Regulatory approval of PPS in the United States[7] was based on the favorable results of 2 clinical trials,[7,8] including one in which patients met the NIDDK definition of IC, including cystoscopic, cytological and biopsy criteria.[8]

We report the results of a dose ranging study performed to satisfy a post-marketing commitment made to the United States FDA upon the approval of PPS. The purpose was to explore the lowest effective PPS dose for IC/BPS treatment.

MATERIALS AND METHODS

Ethical Practices

At each participating hospital an independent review board in the United States or a research ethics board in Canada reviewed and approved the study protocol and its amendments. The study was done in accordance with the ethical principles originating in the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written informed consent before study participation. The study is registered at ClinicalTrials.gov (NCT 00086684).

Patients

Study participants were men and women 18 years old or older with IC/BPS based on a total score of 8 or greater on ICSI and a score of greater than 0 on each component item (bladder pain, urinary urgency, frequency and nocturia)[9] that was unrelated to urinary tract infection for at least 6 months before screening. Eligible patients experienced an average of at least 10 voids per day (ie 30 or greater voids during 3 consecutive days), of which 1 or more were during the night (ie a score of 1 or greater on ICSI item 3).

Key eligibility criteria also required that patients had not received intravesical therapy (eg bladder distension or dimethyl sulfoxide) or undergone cystoscopy during the 4 weeks before screening. They had no evidence of microscopic hematuria or evaluation positive for significant urological disease within the prior year. In addition, they had not received drugs known to affect IC/BPS symptoms (ie antidepressants, antihistamines, antispasmodics or anticholinergics) within the 4 weeks before screening.

Study Design

This randomized, double-blind, placebo controlled, multicenter study was performed between September 2003 and June 2011. Patients were enrolled in the study at 67 sites, including 52 in the United States and 15 in Canada.

Eligible patients were randomized to PPS 100 mg QD, PPS 100 mg TID (the FDA approved dose) or matching placebo in a 1:1:1 ratio based on a computer generated randomization schedule. Randomization was balanced using randomly permuted blocks and stratified by whether patients had or had not ever been treated with PPS. The double-blind treatment period was 24 weeks. Concomitant use of drugs known to affect IC/BPS symptoms was restricted to 28 days or less as needed for exacerbation.

Efficacy Assessments

Patients rated the presence and extent of IC/BPS symptoms, including urinary urgency, urinary frequency (derived as an average number of daily events from the 24-hour urinary record collected during the 3 consecutive days before baseline), nocturia and pain/burning in the bladder, by completing the validated, 4-item self-administered ICSI questionnaire[9] at baseline, and at weeks 4, 8, 12, 18 and 24. On the 5-point numerical rating scale higher scores indicated worse symptoms (1—not at all to 5—almost always on items 1, 2 and 4, and 5—5 or more times per night on item 3). At the same time points patients also rated average bladder pain intensity during the previous 3 days using an 11-point numerical rating scale of 0—no pain to 10—worst possible pain. PORIS was administered to patients at all visits after baseline to measure pain, urgency and the overall change compared to before study drug initiation. There was 1 question for each of pain, urgency and overall change with 6 choices ranging from worse to symptoms resolved. At study end patients rated overall status since beginning the study medication (ie GRA) using a 7-point numerical rating scale of 1—markedly worsened to 7—markedly improved.