Targeting the SHIP1 Pathway Fails to Show Treatment Benefit in Interstitial Cystitis/Bladder Pain Syndrome: Lessons Learned from Evaluating Potentially Effective Therapies in This Enigmatic Syndrome

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Purpose: In this 12-week, randomized, double-blind, placebo controlled, multicenter, 3-arm, parallel group, phase 3 trial we assessed the effects of a novel SHIP1 activator on bladder pain and urinary symptoms in patients with interstitial cystitis/bladder pain syndrome.

Materials and Methods: Subjects with interstitial cystitis/bladder pain syndrome and a mean pain score of 5 or greater on an 11-point scale despite treatment were randomized to 100 or 200 mg of an oral SHIP1 activator or placebo once daily for 12 weeks. Maximum pain scores and urinary frequency were recorded in an e-diary. The ICSI (O'Leary-Sant Interstitial Cystitis Symptom Index) and BPIC-SS (Bladder Pain Interstitial Cystitis Symptom Score) questionnaires were administered. Safety was monitored through 12 weeks of treatment.

Results: A total of 298 female subjects with moderate to severe symptoms of interstitial cystitis/bladder pain syndrome were treated with 100 or 200 mg SHIP1 activator orally once daily for 12 weeks. Treatment demonstrated no difference in maximum daily bladder pain compared to placebo. There was no treatment benefit over that of placebo in the secondary end points of urinary voiding frequency, the BPIC-SS, the ICSI and a global response assessment. Exploratory analysis in 87 male subjects yielded a similar result, that is no difference from placebo. Treatment was generally well tolerated at both doses.

Conclusions: SHIP1 activation is a safe but ineffective therapeutic approach to interstitial cystitis/bladder pain syndrome. Although this was a negative trial, the important lessons learned from this study in respect to inflammatory phenotype differentiation, including the potential importance of cystoscopy based classification, will improve current treatment in patients with interstitial

Abbreviations and Acronyms

BPIC-SS = Bladder Pain IC Symptom Score

FDA = Food and Drug Administration

IC = interstitial cystitis

IC/BPS = IC/bladder pain syndrome

ICSI = O'Leary-Sant IC Symptom Index

NRS = numerical rating scale

RCT = randomized controlled trial

SHIP1 = SH2-containing inositol-5'-phosphatase 1 activator

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cystitis/bladder pain syndrome and allow for better future trial design in those with this difficult urological chronic pain syndrome.

Key Words: urinary bladder; cystitis, interstitial; pelvic pain; patient reported outcome measures; negative results

Interstitial cystitis/bladder pain syndrome is a chronic condition of unknown etiology involving bladder pain and usually urinary urgency, frequency and nocturia.[1,2] The diagnosis is made by excluding other conditions which could cause similar symptoms, such as infection.[1,2] It is more prevalent in women than men,[2] negatively impacts quality of life[1–3] and is associated with psychological disorders[3] and increased health care costs.[4] There is a large unmet need since no pharmacological treatments have proved effective as a general therapy in most patients with IC/BPS.[1,2,5]

A new pharmaceutical class of compounds which activate SHIP1 protein, a modulator of phosphoinositide signaling for diverse processes including cell growth, activation and immune/inflammatory regulation,[6,7] appeared to be a potentially effective therapy in women diagnosed with IC/BPS. A total of 69 women with moderate to severe symptomatic bladder pain and significant levels of other urinary symptoms, including frequency, urgency and nocturia, enrolled in an initial phase II pilot study to evaluate this intervention for IC/BPS.[8] The oral SHIP1 activator AQX-1125 administered once daily at a dose of 200 mg for 6 weeks reduced pain, voiding frequency and IC/BPS symptoms. IC/BPS symptoms, including mean maximum daily bladder pain, dysuria, urinary frequency, urgency, nocturia and bladder pressure or discomfort, were significantly reduced as measured by NRS pain scales and IC/BPS specific symptom questionnaires, including the BPIC-SS,[9] and the ICSI and/or ICPI (Interstitial Cystitis Problem Index).[10] The favorable and exciting results of this phase II RCT prompted the initiation of the current much larger, longer phase III dose ranging RCT to evaluate the therapeutic benefit of this potentially effective SHIP1 activator for IC/BPS.

MATERIALS AND METHODS

This multicenter, phase 3 trial (ClinicalTrials.gov NCT02858453) included a 12-week randomized, double-blind, placebo controlled, parallel group treatment period to compare the efficacy and safety of 2 doses (100 or 200 mg) of AQX-1125 vs placebo. The trial was approved by central and site specific Institutional Review Boards if required.

Subjects 18 to 80 years old with a diagnosis of IC/BPS for more than 6 months were eligible for study enrollment if they met inclusion criteria. The criteria were baseline mean bladder pain 5 or greater on an 11-point scale, BPIC-SS score[9] 19 or greater, a baseline combined ICSI/ICPI[10] score 7 or greater, at least 8 urinary voids per 24 hours, pelvic floor pain less than 7 of 10 following a pelvic pain assessment and receipt of cystoscopy within the last 36 months prior to baseline. Supplementary methods 1 (https://www.jurology.com) shows complete study selection criteria.

Patients were evaluated for eligibility at screening visit 1 and, if required, for cystoscopy at visit 1a (supplementary methods 1, https://www.jurology.com). If all entry criteria were met at baseline visit 2, the subject was randomized to receive a single daily oral dose of 2 tablets for 12 weeks, including AQX-1125, 2 × 100 mg tablets; AQX-1125, 1 × 100 mg + 1 × placebo tablets; or 2 × placebo tablets.

Each subject was trained to use an e-diary to record maximum and average daily bladder pain scores, daily use of rescue pain medications and voiding frequency in a 24-hour period before baseline (visit 2), followed by visits at week 6 (visit 3) and week 12 (visit 4). Subjects completed the BPIC-SS, the ICSI and a general response assessment, the latter at visit 4 only. They underwent a safety assessment at each visit.

Analysis

The primary analysis was based on all efficacy data on female subjects based on the results of the initial study and safety data on all subjects who completed the 12-week study. The study primary end point was the maximum daily bladder pain score, considered maximum scores on a standardized 11-point NRS recorded in the e-diary once daily for a minimum of 5 of 7 days prior to each visit, as determined by the change from baseline (visit 2) at week 12 (visit 4) for AQX-1125, 100 or 200 mg, compared to placebo. The key secondary end points were the mean change from baseline (visit 2) at week 12 (visit 4) for AQX-1125, 100 or 200 mg, compared to placebo in voiding frequency and scores on the ICSI and the BPIC-SS. The overall response to treatment for AQX-1125, 100 or 200 mg, compared to placebo was measured by the subject global response assessment at week 12.

Safety

The frequency and severity of adverse events were coded using the most recent version of the MedDRA (Medical Dictionary for Regulatory Activities). This included ocular events reported during the comprehensive ophthalmic examinations mandated by the FDA.

Statistical Methods

Sample size calculation was based on the female population in which 86 female subjects per group would have 90% power to detect a 1.0-point improvement in the change from the baseline maximum pain score in either or both AQX-1125 dose groups compared to the placebo group, assuming a common SD of 2.0 and using the 2-sided t-test and a 5% significance level. Assuming a

15% dropout rate a minimum of 300 female subjects (100 per treatment arm) was planned to be randomized. Randomization was stratified by gender and a recent (less than 36 months) history of a positive Hunner lesion. All statistical tests were 2-sided and performed at the 5% significance level unless otherwise stated, using SAP®, version 4.0.

RESULTS

A total of 433 subjects with IC/BPS, including 341 females and 92 males, were randomized across 86 clinical research centers in North America and Europe, of whom 385 completed treatment, including 298 females and 87 males (fig. 1). Demographics and baseline characteristics were evenly distributed between the groups (tables 1 and 2).

The study failed to achieve the primary end point, defined as a change from baseline at week 12 in the maximum daily bladder pain score (fig. 2). Analyses were done to compare placebo in 114 subjects vs AQX-1125, 100 mg in 114 vs AQX-1125, 200 mg in 113. No difference between any treatment arms was significant ($p = 0.41$), nor were pairwise comparisons significant in female subjects, including placebo vs AQX-1125, 100 mg and placebo vs AQX-1125, 200 mg in female subjects ($p = 0.16$ and 0.41, respectively, table 3). The study also failed to demonstrate a benefit of AQX-1125 over placebo for each of the 3 predefined secondary end points of urinary voiding frequency, the BPIC-SS and the global response assessment.

Multiple sensitivity analyses were done on the primary end point, including a repeat of the primary mixed effects growth curve model using all available e-diary data, an ANCOVA modeling approach with last observation carried forward for all observations, an unadjusted parsimonious mixed effects growth curve model, a complete case mixed effects growth curve model and a multiple imputation model. All analyses yielded consistent results in directionality and in effect magnitude. Subgroup analyses using the primary analysis method done in female subjects also did not show a treatment benefit in any of the predefined subgroups, including geographic region, high vs low enrolling centers, Hunner lesion presence or absence, disease duration, baseline pain level or urination frequency, presence or absence of other chronic pain conditions, concomitant IC/BPS treatments at baseline, age, race or ethnicity and baseline body mass index. Exploratory analysis of the primary end point in male subjects similarly did not differentiate AQX-1125 from placebo (data not shown).

AQX-1125 was generally well tolerated at the 100 and 200 mg doses. Overall adverse event rates were similar in the placebo group and the 2 AQX-1125 treatment groups, including treatment emergent adverse events, serious adverse events and treatment emergent adverse events of special interest such as ocular events (supplementary table, http://www.jurology.com). Supplementary methods 2

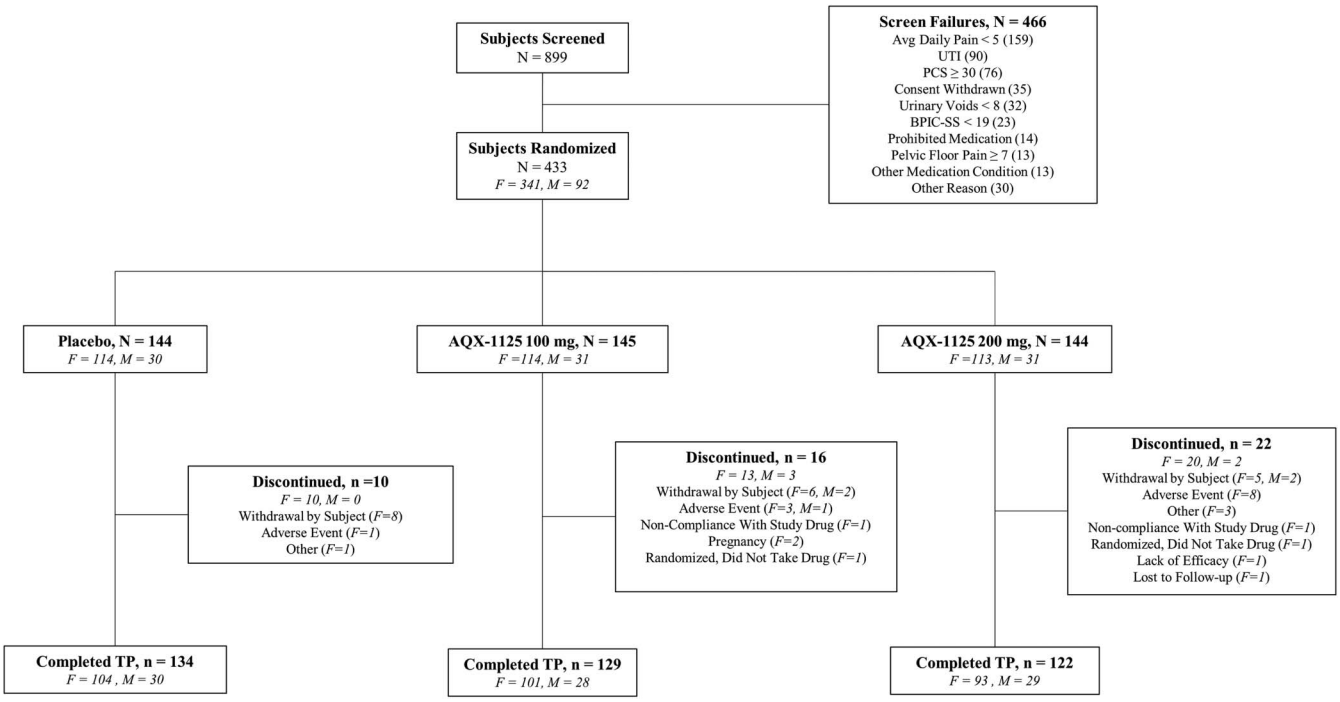

Figure 1. Study subject disposition. Because subjects may have had multiple reasons for not being enrolled in study, sum of reasons for screen failure may be greater than number of subjects with screen failure. *UTI*, urinary tract infection. *PCS*, polycystic ovary syndrome. *TP*, treatment period.

Table 1. *Summary of baseline demographic characteristics in female subjects*

	Placebo	AQX-1125 (mg) 100	AQX-1125 (mg) 200	Overall
No. pts	114	114	113	341
Mean ± SD age/median (range)	47.7 ± 15.10/47.0 (18–78)	50.1 ± 15.17/51.5 (18–80)	49.7 ± 14.84/50.0 (20–78)	49.2 ± 15.03/49.0 (18–80)
No. race (%):				
American Indian or Alaska Native	1 (0.9)	0	1 (0.9)	2 (0.6)
Asian	1 (0.9)	0	0	1 (0.3)
Black or African American	5 (4.4)	5 (4.4)	4 (3.5)	14 (4.1)
Native Hawaiian or other Pacific Islander	0	0	1 (0.9)	1 (0.3)
Caucasian	107 (93.9)	108 (94.7)	106 (93.8)	321 (94.1)
Multiple	0	1 (0.9)	1 (0.9)	2 (0.6)
No. ethnicity (%):				
Hispanic or Latino	5 (4.4)	8 (7.0)	5 (4.4)	18 (5.3)
Not Hispanic or Latino	107 (93.9)	106 (93.0)	107 (94.7)	320 (93.8)
Not reported	2 (1.8)	0	1 (0.9)	3 (0.9)
Unknown	0	0	0	0
Mean ± SD kg/m^2 body mass index/median (range)	27.2 ± 6.17/26.0 (17–50)	26.3 ± 6.11/25.0 (14–49)	27.3 ± 6.35/26.0 (16–48)	26.9 ± 6.21/26.0 (14–50)
Mean ± SD yrs IC/BPS diagnosis history/median (range)	3.83 ± 4.32/1.96 (0.2–19.7)	5.27 ± 4.80/3.58 (0.1–19.8)	4.78 ± 5.08/2.75 (0.1–24.9)	4.63 ± 4.77/2.75 (0.1–24.9)
No. Hunner lesion (%):				
Present	25 (21.9)	23 (20.4)	24 (21.2)	72 (21.2)
Absent	89 (78.1)	90 (79.6)	89 (78.8)	268 (78.8)
Missing	0	1	0	1

Percents are based on number of patients with nonmissing answer.

Table 2. *Summary of baseline efficacy assessments in female subjects*

	Placebo	AQX-1125 (mg) 100	AQX-1125 (mg) 200
No. pts	114	114	113
Max daily pain:			
No. pts	114	113	113
Mean ± SD/median (range)	7.36 ± 1.179/7.43 (4.00—10.00)	7.44 ± 0.995/7.43 (5.00—9.86)	7.26 ± 1.160/7.43 (4.00—10.00)
Av daily pain:			
No. pts	114	113	113
Mean ± SD/median (range)	6.45 ± 1.040/6.29 (3.50—9.86)	6.45 ± 0.967/6.29 (5.00—8.86)	6.35 ± 1.011/6.29 (3.14—9.14)
Urinary voiding frequency:			
No. pts	114	113	111
Mean ± SD/median (range)	18.61 ± 11.014/15.00 (8.00—77.00)	19.83 ± 11.077/16.00 (2.00—60.00)	18.95 ± 10.621/17.00 (8.00—72.00)
BPIC-SS:			
No. pts	114	112	113
Mean ± SD/median (range)	27.61 ± 4.485/28.00 (16.00—36.00)	28.33 ± 4.445/28.00 (18.00—37.00)	27.88 ± 4.367/28.00 (17.00— 36.00)

(https://www.jurology.com) shows an expanded discussion.

DISCUSSION

Despite the exciting results from the first RCT evaluating this novel approach to treating IC/BPS,[8] the current 12-week, randomized, multicenter, double-blind, placebo controlled, 3-arm, parallel group, phase 3 trial failed to demonstrate efficacy of targeting the SHIP1 pathway in subjects with IC/BPS. While the safety of this intervention observed in the first trial was confirmed, the clinical meaningful benefits in female patients with IC/BPS in whom traditional therapy had failed was not confirmed. In fact, the trial failed to meet any a priori primary and/or secondary end points, or any end points in the exploratory analyses done in female and male subjects. Further analyses revealed that the discrepancy between the initial study and the current pivotal trial was not the result of enrollment outside North America or by high enrolling trial centers, or nonacademic or nonIC centers. What lessons were learned which could prove useful for evaluating future clinical interventions for this difficult urological chronic pain syndrome?

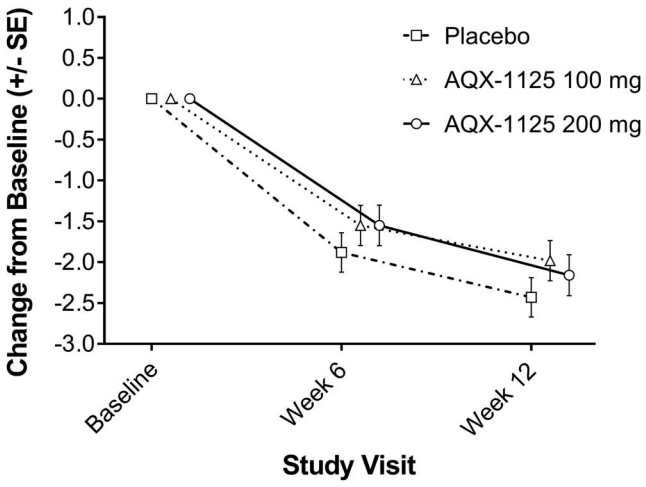

Figure 2. Least square mean ± SE mixed effects growth curve model change from baseline in maximum daily bladder pain NRS score during treatment phase in female intent to treat population, which was primary end point. Subjects recorded maximum daily bladder pain in e-diary using 1-time 11-point NRS of 0—no pain to 10—"pain as bad as you can imagine." Minimum of 5 of 7 values before each visit were averaged to determine NRS at each visit.

The debate in regard to the potential benefits of various treatment modalities will continue until we know more about IC/BPS pathophysiology. Currently most prescribed pharmacotherapies treat systemic symptoms (pain) or attempt to repair, coat or anesthetize the bladder lining through intravesical instillations.[1,2] None of these approaches has proved successful as a general therapy in all patients with IC/BPS.[1,2,5] The approach of using the novel anti-inflammatory mechanism of SHIP1 activation, a mechanism which looked so promising at the first evaluation,[8] did not reduce pain or any other urinary symptoms in this trial.

The search for effective therapies for patients with IC/BPS has a history of the excitement of potentially effective therapies based on small studies, usually from a single center, leading to the initiation of ambitious multicenter RCTs which fail to meet therapeutic end points. This experience has been evident for various intravesical treatment approaches, such as bacillus Calmette-Guérin,[11] resiniferatoxin[12] and chondroitin sulfate[13] RCTs, perhaps because of higher than expected placebo effects due to the expectations of physical intervention. Unfortunately the same experience was evidenced in recent large, well powered RCTs evaluating potentially beneficial oral therapies, including tanezumab,[14] pentosan polysulfate sodium,[15] amitriptyline[16] and Ca^{2+} channel $\alpha 2\delta$ ligand[17] as well as mycophenolate mofetil immunotherapy.[18]

Table 3. *Efficacy results, and primary and key secondary end points in female subjects*

	Mean Baseline Wk 12 Change			AQX-1125 vs Placebo Least Squares Mean Difference (95% CI)		
	Placebo	AQX-1125 100 mg	AQX-1125 200 mg	AQX-1125 100 mg	AQX-1125 200 mg	p Value (global test)
No. pts	114	114	113	—	—	—
Daily pain:						
Max	−2.52	−2.07	−2.26	0.45 (−0.18−1.08)	0.27 (−0.37−0.90)	0.4052
Av	−2.47	−1.96	−2.02	0.47 (−0.10−1.05)	0.44 (−0.14−1.02)	0.2575
Voiding frequency	−5.93	−4.83	−5.29	1.83 (−0.21−3.88)	1.17 (−0.92−3.26)	0.3111
BPIC-SS	−7.53	−7.15	−7.20	0.46 (−1.58−2.49)	0.36 (−1.71−2.42)	0.8446

The discrepancies between the efficacy observed in early studies and the negative followup RCTs lend credence to the unavoidable fact that we really do not understand IC/BPS enough at this stage to design a truly effective, mechanism based therapy for all patients. We must learn the lessons of our failed clinical trials to help us move forward in evaluating new therapies and effectively treat patients with the therapies we now have available.

One of the clear messages that these trials have taught us is that it is difficult to evaluate an intervention for a syndrome based on subjective outcomes (pain) and the exclusion of other diseases which cause similar symptoms.[1] Except for perhaps the Hunner lesion subgroup[19] we should not consider IC/BPS a disease but rather a syndrome. The diagnosis does not include defining objective clinical parameters which lead to a more accurate diagnosis and/or targets for intervention. It becomes challenging to target a mechanism when we do not really know the mechanism responsible for the chronic pain and the urinary symptoms.

It is likely that IC/BPS is a heterogeneous condition in which patients with these symptoms fall within a continuous spectrum or individual unique phenotypes associated with inflammatory, neuroinflammatory (with or without neuroendocrine) and/or neurogenically mediated disease states which may evolve with symptom chronicity. This range of conditions is likely anchored on one end by the Hunner lesion IC variant with its distinct, observable inflammatory lesions and predictable pathological features.[19] The middle spectrum of disease likely involves various neuroinflammatory states, including neuroendocrine mechanisms, or systemic or local (mast cells) manifestations.[20] This variable phenotype might be associated with increased mast cells in the bladder wall (the submucosa as well as the detrusor muscle)[20] and/or systemic endocrine changes (abnormal cortisol fluctuations).[21] The bladder wall may show hyperemia, even a wheal and flare reaction to a cystoscope touching the bladder wall, or glomerulations with or without bladder distension. The other end of the spectrum or range of conditions, which is associated with no observable bladder pathology but definite bladder mucosal hypersensitivity, is probably mediated primarily through local and/or centralized neurogenic mechanisms.[22] One or many of these mechanisms may be operative in an individual patient to produce a unique personal clinical picture or phenotype.

To further complicate the development and evaluation of a new intervention these mechanisms causing bladder pain and urinary symptoms are mediated by hormone fluctuations such as the estrogen menstrual cycles in women,[23] spinal cord crosstalk with other pelvic organs such as the lower bowel[24] and the pelvic floor,[25] and psychosocial parameters[3,26] such as depression, stress, anxiety and the effectiveness of individual coping skills.[27]

Chronic medication washout is difficult in IC/BPS trials because of enrollment difficulties, in that many patients would not accept this requirement. Also, even if only perceived by the patient, the resulting change in symptoms after discontinuing stable medications could bias the final outcome.

Finally, patients do not present only with bladder pain and urinary symptoms. The clinical picture of at least 80% of patients with IC/BPS includes symptoms of other local pelvic pain conditions such as pelvic floor dysfunctional pain and vulvodynia,[25] and systemic enigmatic pain conditions such as irritable bowel syndrome and fibromyalgia.[28] A major clue that phenotype is important is that the subjects enrolled in this trial differed from those enrolled in the initial trial in which there was a demonstrable treatment effect across almost all measures of efficacy.[8] To be enrolled in the first study patients had to have documented visible signs of bladder bleeding, Hunner lesions or glomerulations on cystoscopy within the last 36 months prior to baseline. Although cystoscopy was required in the current RCT, there was no requirement of observable pathology and, if observed, no documentation of active vs previously treated or healed Hunner lesions. However, exploratory analyses in the small and poorly defined Hunner lesion subgroup did not show a treatment effect for SHIP1 activation in the current study.

We should and can address these lessons learned. We must continue our efforts to discover a biomarker enabling better diagnosis of IC/BPS or alternatively better differentiation of subgroups, such as a better cystoscopy classification. The 2018 BRUDAC (Bone, Reproductive and Urological Drugs Advisory Committee) report,[29] a recent attempt to update criteria on the design of IC/BPS treatment trials, also calls for the development of validated instruments to evaluate IC/BPS specific patient reported outcomes.

We need to continue to examine patho-etiology, knowing that different mechanisms or even cascades of mechanisms likely operate in different subgroups of patients with IC/BPS. We must embrace the fact that patients with IC/BPS are not a homogenous group but rather present with different and individual phenotypes. This approach, which has led to better management strategies at IC/BPS dedicated clinics,[30] should now be incorporated in developing clinical trials to evaluate specific interventions. It has been more than 2 decades since a new therapy (pentosan polysulfate sodium) of IC/BPS was approved by the FDA and even that intervention proved to be ineffective in a contemporary RCT evaluation.[15]

We have much to learn not only about the pathophysiology but also the proper phenotyping of this syndrome (eg the relevance of cystoscopy observations). Each will contribute to the development of effective interventions in the future.

CONCLUSIONS

SHIP1 activation is a safe but ineffective therapy in patients with IC/BPS. The lessons of this clinical trial and other large RCTs which failed to meet clinically meaningful end points were learned at huge expense to the sponsors, a significant time commitment from the investigators and a great burden to the subjects enrolled in the studies. We owe it to all involved parties to use these lessons learned not only to better design intervention strategies for future therapies but also to improve our current management of this important urological pain condition.

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EDITORIAL COMMENT

IC/BPS is a heterogeneous syndrome with multiple potential phenotypes and etiologies. Can we really expect 1 treatment to benefit all patients with IC/BPS?

The phenotyping effort showed that IC/BPS may be further subgrouped based on the presence of 1) Hunner lesion(s); 2) pelvic floor myofascial tenderness and hypertonicity on examination; 3) widespread pain and/or chronic overlapping pain conditions such as fibromyalgia, which might be an indicator of central sensitization or top-down systemic pathophysiology;[1] and 4) painful bladder filling and/or painful urgency, which are bladder phenotype markers.[2]

Using a 1 size fits all approach to treat all patients with IC/BPS without regard for phenotype may lead to treatment failures. This may explain why so many randomized, controlled trials, including this one, failed to demonstrate benefits to the heterogeneous population. In fact, the more successful IC/BPS treatments have incorporated this concept of phenotyping to target specific subpopulations of the syndrome. Triamcinolone injection, fulguration and cyclosporine have better results in patients with Hunner lesion (phenotype 1). Myofascial physical therapy works well in female patients with demonstrable pelvic floor tenderness on examination (phenotype 2).[3] Clinicians should stratify these phenotypes when they design and power the next clinical trials.

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REFERENCES

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REPLY BY AUTHORS

The comment summarizes the painfully learned lessons on how to optimally evaluate interventions in IC/BPS. As a urology clinical research community we must use this evolving knowledge when designing treatment trials by matching intervention with mechanism, restricting inclusion and exclusion criteria to match more limited objectives, employing innovative trial design such as adaptive trial design or “N of 1” studies and convincing regulatory authorities (eg the FDA) that 1 size does not fit all. We owe this to ourselves as clinical researchers hoping to design better treatment options, to the sponsors willing to invest in this difficult field and most of all to our patients with IC/BPS, who deserve the best evidence-based treatment potentially available.