Mirabegron as adjuvant treatment for patients with interstitial cystitis/bladder pain syndrome

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Abstract

Introduction: Interstitial cystitis/bladder pain syndrome (IC/BPS) patients represent a heterogeneous group with pain and urinary storage symptoms and varying responses to current treatment options. The novel beta-3 agonist, mirabegron, has been shown to improve storage symptoms of patients with bladder overactivity; however, its effect on symptoms in the IC/BPS population has yet to be studied.

Methods: Patients diagnosed at a single IC centre with IC/BPS undergoing standard therapy were treated with additional daily mirabegron 25 mg and seen in followup post-treatment. Patients completed the Interstitial Cystitis Symptom Index and Problem Index (ICSI/ICPI), and the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF) prior to and following mirabegron treatment. Global (NRS) and symptom-specific outcomes were assessed by comparing the pre- and post-treatment mean scores using tailed-t test ($p<0.05$ considered statistically significant).

Results: A total of 23 patients were available for review pre- and post-mirabegron treatment. There was no significant difference in ICSI ($p=0.448$), ICPI ($p=0.352$), or PUF ($p=0.869$) pre- and post-treatment. Analysis of symptom-specific outcomes show statistically significant improvements in urgency ($p=0.048$); however, no statistically significant improvements in frequency ($p=0.951$) or pain ($p=0.952$) were observed with mirabegron therapy.

Conclusions: IC/BPS patients treated with mirabegron had improvement of urinary urgency, but no significant benefit in terms of pain or urinary frequency. This data suggests that mirabegron's role in the IC/BPS patient should be that of adjuvant treatment to ameliorate urgency.

Introduction

Interstitial cystitis (IC), or bladder pain syndrome (BPS), is a chronic disease characterized by suprapubic pain related to bladder filling, coupled with additional symptoms, including increased urinary frequency or urgency, without proven urinary infection or obvious pathology.[1-3] The symptoms typically associated with IC often overlap with other gynecological and urological conditions, including overactive bladder (OAB), which is characterized by urinary urgency, with or without urge urinary incontinence, usually with frequency and nocturia but no pain.[4] Patients diagnosed with IC/BPS comprise a diverse group of patients with varied clinical phenotypes[5-7] and the presence of various other comorbid chronic pain and symptom-based syndromes has been widely reported.[8-10] The heterogeneity of this patient population suggests that IC/BPS, instead of existing as one diagnosable entity, is more likely a combination of etiologies with a varied pathogenesis and symptom patterns. Given its diverse clinical phenotype, appropriately managing these patients' symptoms has historically been difficult and the current goals of treatment are largely based on symptomatic relief. At present, a number of treatments are available for IC/BPS, including conservative measures, oral medical therapy, intravesical drug instillation, hydrodistention, neuromodulation, and surgical therapy.[11] Although several therapies have been shown to help the symptoms of IC/BPS in clinical trials, multimodal therapy may be the most effective approach in dealing with the range of IC symptoms.[12]

One of the more common and bothersome symptoms in the IC/BPS population is that of urinary urgency.[13] As urgency is considered to be the characteristic symptom of overactive bladder, its presence often confounds and delays the diagnosis and treatment of IC/BPS. Given the reports of qualitative differences in the urgency experienced by IC/BPS patients compared to OAB patients,[14,15] the pathophysiology behind this symptom's development may not be similar. Although, anticholinergics are well-established as pharmacotherapy for reducing OAB symptoms,[16] classic anticholinergic and bladder antispasmodics have shown not to be efficacious in regards to these symptoms in the IC/BPS population.[17,18]

The novel bladder antispasmodics, mirabegron, targets an alternative pathway to achieve control of urinary storage

dysfunction. Recent advances in the understanding of the physiopathology of OAB have identified three subtypes of b-adrenoceptor (b1, b2, and b3) in the detrusor muscle and urothelium,[19-21] of which b3-adrenoceptors predominate. The stimulation of the b3 subtype is thought to be the main subtype responsible for mediating relaxation of the detrusor in humans.[22] Mirabegron is the first b3-adrenoceptor agonist to enter clinical practice and has been approved for the treatment of symptoms of OAB, including urinary frequency, urgency, and urge incontinence. As mirabegron has been shown to be successful in treating the urgency and frequency symptoms in patients with OAB, it may also provide a potential efficacious treatment for the IC/BPS patient population. To our knowledge, the use of mirabegron has yet to be reported in this specific population. Our objective was to provide preliminary real-life clinical practice data of effectiveness outcomes of mirabegron in patients with IC/BPS.

Methods

Participants and study design

The current report is a prospective evaluation of IC/BPS patients treated at a single outpatient clinic in a real-life clinical practice setting. This study was an open-label design where the patients were not blinded to treatment. Clinical features of our patients included chronic (for at least six months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom, such as persistent urge to void or frequency. Patients fulfilled the recent IC/BPS definition in the American Urological Association (AUA) guidelines.[11]

Exclusion criteria included vesical and urethral pathologies (urinary tract infection, neurogenic bladder, urethral diverticula, bladder or urethral cancer, urinary stones, urge/stress incontinence, pelvic prolapses) or non-urological pathologies (vaginitis, uterine, vaginal or cervical cancers, endometriosis) not related to IC/BPS, or previous/current treatment with mirabegron prior to enrollment.

Patients with IC/BPS with bothersome storage symptoms that did not respond to an anticholinergic trial were offered mirabegron 25 mg daily as add-on therapy. Patients continued on standard therapy as prescribed. As part of the clinic protocol, all patients underwent standard assessment, which includes history and physical exam and completion of validated questionnaires before and after any treatment intervention. Prospective data was collected as part of our ongoing IRB-approved quality assurance audit process. Patients were de-identified before inclusion in this protocol data base.

Patients were re-assessed at the time of their routine clinic appointments and participants underwent standardized clinic repeat assessment and completion of IC/BPS questionnaires.

Measures

Demographics and self-reported symptom history

Demographics, self-reported symptom history (including duration of IC/BPS symptoms), and concurrent medications were collected as standard clinic routine.

Condition-specific symptom questionnaires

IC/BPS-specific symptoms were evaluated by the validated Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI),[23] Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF),[24] numerical rating scale (NRS) pain, NRS urgency, and NRS frequency scores. These instruments are routinely collected before and after any treatment change. Pre- and post-treatment questionnaires were analyzed and reported with a global score. In addition, questions corresponding to specific symptom parameters (pain, urinary urgency, urinary frequency) were identified and scores pre- and post-treatment were assessed.

Data analysis

Statistical analysis was completed using Microsoft Excel 2010 Data Analysis package and R – version 3.3.1. All questionnaire scores collected at first post-treatment visit was compared to mean baseline scores using a Wilcoxon ranked-sign test assuming unequal variances. All results were regarded as statistically significant at p=0.05.

Results

Patient demographics

Twenty-eight patients completed standardized clinic questionnaires before and after mirabegron add-on treatment was initiated. Of the twenty-eight patients, five were prescribed, but did not take mirabegron and were excluded from final analysis. Patient demographics for the 23 IC/BPS patients are depicted in Table 1. Patients were predominantly female (n=22, 95.7%) and Caucasian (n=22, 95.7%) with a mean age of 49.0 years. Standard duration between pre- and post-treatment assessments was 6.9 months. Of the patients who had information available regarding length of symptom duration (n=15), the average IC/BPS patient had experienced symptoms 10.5 months prior to mirabegron treatment.

Concurrent therapy of BPS/IC patients pre- and post-treatment

Table 2 lists the concomitant treatments of patients for their IC/BPS symptoms during mirabegron treatment period. All

Table 1. Patient demographics (n=23)

	Mean	SD	Median	IQR
Age	48.96	±13.5	49	20.5
Symptom duration (months)	10.47	±10.8	5	13.5
Months between visits	6.9	±4.0	6	3.5
Sex				
Female	22	95.6%		
Male	1	4.4%		
Race				
Caucasian	22	95.6%		
Other	1	4.4%		

IQR: interquartile range; SD: standard deviation.

patients (n=23) enrolled in the study were taking first- and second-line treatment recommendations as outline by AUA guidelines. Of note, one patient stopped intravesical lidocaine and another initiated Botox injections during the course of the study.

Mirabegron was well-tolerated by the IC/BPS patient population. All patients who initiated mirabegron therapy remained compliant on the medication during the course of the study. Of the 23 patients enrolled, four patients noted adverse effects believed by patient to be caused by mirabegron treatment. One patient noted increase in blood pressure, another reported headaches, and two noted increased difficulty voiding.

Global and symptom-specific questionnaire scores pre- and post-treatment

Table 3 lists the pre- and post-treatment total score of the questionnaires. There was no significant difference in total scores of ICSI, ICPI, or PUF of patients pre- and post-treatment with mirabegron. When subcategorizing the PUF questionnaire to symptom score and bother score, no statistically significant difference was identified following treatment.

In terms of discrete symptoms measures (Table 4), there was a statistically significant improvement in urgency measures gathered from the ICSI questionnaire (p=0.0102). No statistically significant difference was seen in the pain (p=0.9823) and frequency (p=0.9293) domains of the questionnaires.

Table 2. Ongoing therapy of IC/BPS patients during mirabegron treatment (n=23)

Therapy	n	%
Diet modifications	19	82.6
Antidepressants	8	34.8
Pentosan polysulfate	8	34.8
Pelvic floor physiotherapy	4	17.4
Massage/yoga	3	13.0
Psychotherapy pain program	2	8.7
Gabapentinoids	2	8.7
Pyridium	2	8.7
Lidocaine[1]	1	4.3
Sodium citrate	1	4.3
Botox injections[2]	1	4.3

[1]Started after mirabegron administration. [2]Stopped prior to completion of study.
IC/BPS: interstitial cystitis/bladder pain syndrome.

Discussion

In recent large phase 3 clinical trials, mirabegron has demonstrated significant efficacy over placebo in treating the symptoms of OAB, including micturition frequency, urgency incontinence, and urgency.[25,26] Given IC/BPS's similar overlying symptomatology with OAB in terms of urgency-related symptoms, we hypothesized that mirabegron may also play a role in treating that subset of symptoms in the IC/BPS population. The analysis of our prospectively collected, real-life clinical practice data from a single centre IC/BPS patient population shows that mirabegron may improve urgency symptoms in patients with IC/BPS, however, showed no significant improvement in frequency or pain symptoms. Furthermore, no significant improvement was noted in the total scores of the disease-specific ICSI, ICPI, and PUF questionnaires.

Although the symptoms of urgency and frequency are described by both OAB and IC populations, there may be a qualitative difference in the way these symptoms are experienced. IC/BPS patients may experience a more constant urge to void as opposed to the ICS definition of a "compelling need to urinate, which is difficult to postpone."[27] The prototypical OAB patients urge to void is driven to prevent episodes of incontinence; however, in the IC/BPS population, patients void to stop or to relieve pain. Overall the patients perceive some improvement in urgency not cor-

Table 3. Total scores before and after mirabegron treatment (n=23)

		Before treatment		After treatment		p
		Median	IQR	Median	IQR	
Total scores	ICSI total	12	6	12	5.5	0.554
	ICPI total	10	3.5	10	5	0.313
	PUF total	18	6	19	8.5	0.991
	Symptom score total PUF	13	4.5	12	5.5	0.834
	Bother score total PUF	6	3	6	3	0.894

ICPI: Interstitial Cystitis Problem Index; ICSI: Interstitial Cystitis Symptom Index; IQR: interquartile range; PUF: Pelvic Pain and Urgency/Frequency Patient Symptom Scale.

Table 4. Symptom-specific scores before and after mirabegron treatment (n=23)

		Before treatment		After treatment		p
		Median	IQR	Median	IQR	
Pain	Pain NRS	6	3.5	6	4	0.9823
Frequency	Frequency NRS	7	3.5	7	3.5	0.9293
	Urinate less than 2 hours after coid ICSI	4	2	4	3	0.8615
	Frequent urination day ICPI	3	0.5	3	2	0.7897
	Bathroom count per day PUF	2	2	2	1.5	0.5336
Urgency	Urgency NRS	7	2	5	3	0.0717
	Urinate with no warning ICSI	4	1.5	2	3	0.0102
	Need urinate little warning ICPI	3	1	2	2	0.6209
	Urgency rating PUF	2	1.5	1	2	0.6541

ICPI: Interstitial Cystitis Problem Index; ICSI: Interstitial Cystitis Symptom Index; IQR: interquartile range; PUF: Pelvic Pain and Urgency/Frequency Patient Symptom Scale.

roborated by the specific urgency-associated questions. As mirabegron is primarily targeted at motor relaxation of the detrusor muscle and not bladder sensation, this may explain mirabegron's efficacy at treating the urgency in the OAB population compared to the IC/BPS subgroup and, therefore, the limited benefit seen in this study.

Pain and discomfort is also a significant symptom in IC/BPS. However, our knowledge of the afferent mechanisms that determine perceptions of lower urinary tract symptoms is limited. It is known that afferent sensory receptors of the urothelium of the bladder communicate with the central nervous system via finely mylenated A-delta fibers and unmylenated C-fibers. A-delta fibers sense bladder filling and tension within the bladder wall, whereas C-fibers transmit discomfort or pain in response to excessive stretching of the bladder wall. A study performed by Aizawa et al[28] found that mirabegron can inhibit bladder afferent activity of A-delta fibers and C-fibers in a dose-dependent fashion. Via inhibition of these afferent pain fibers, it was anticipated that mirabegron may decrease the sensation of pain associated with IC/BPS. Despite this, we were not able to show any significant reduction in pain following mirabegron administration. It is conceivable that pain reduction by other IC/BPS treatments could potentiate the benefits in terms of urgency improvement, but our analysis was not powered to show such an effect.

The findings of this study must be interpreted in the context of real-life clinical setting rather than a prospective clinical trial design. Given then real-world design, this study was not without limitations, which include the limited sample size and subsequent low power. Furthermore, as this was a real-world evaluation, patients enrolled were on concurrent medications in addition to starting mirabegron therapy, as well as unblinded to treatment. The effect of synergistic treatment with mirabegron is difficult to ascertain given the heterogeneity in treatment baseline. Furthermore our patient population has previously been assessed and optimally treated prior to starting mirabegron as an add-on. Perhaps mirabegron may be more effective in newly diagnosed IC/BPS patients with early storage symptoms and mild pain.

Given the results of our current observations, we cannot recommend a large, double-blind, placebo-controlled clinical trial to assess the efficacy of mirabegron as monotherapy and it would be difficult to design a study evaluating it as an add-on or adjuvant treatment. That being said, it seems reasonable to consider initiating mirabegron as an adjuvant treatment in patients who continue to have bothersome urgency despite standard IC/BPS therapy.

Conclusion

Our study was the first evaluation of daily low-dose mirabegron therapy for IC/BPS. Despite the limitations of this analysis, the outcomes suggest that mirabegron currently plays a limited role in the treatment of urgency, but not the pain associated with IC/BPS.

Competing interests: Dr. Nickel has been a consultant for Astellas, Auxillium, Eli Lilly, Farr Labs, Ferring, GSK, Pfizer, Taris Biomedical, Tribute, and Trillium Therapeutics; a lecturer for Astellas and Eli Lilly; and has participated in clinical trials supported by Eli Lilly, GSK, J&J, Pfizer, and Taris Biomedical. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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