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BPS/INTERSTITIAL CYSTITIS (D CASTRO-DIAZ AND Y IGAWA, SECTION EDITORS)

Immunomodulatory Therapies for Interstitial Cystitis/Bladder Pain Syndrome

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Abstract

Purpose of Review Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic, debilitating condition of unknown etiology characterized by persistent pain perceived to be related to the urinary bladder and lower urinary tract symptoms. Evidence shows that immunological inflammatory responses underlie the pathophysiology of IC/BPS with Hunner lesions but not that of IC/BPS without Hunner lesions. Here, we review the current understanding of the immunological inflammatory nature of IC/BPS with Hunner lesions and the clinical outcomes of immunomodulatory therapies.

Recent Findings Open trials show that steroids improve validated symptom scores and pain scale score markedly in patients with IC/BPS with Hunner lesions. Open trials and a randomized study show that cyclosporine A improves urinary frequency, pain intensity, and bladder capacity significantly in IC/BPS patients, showing therapeutic superiority in the Hunner lesion subtype. A randomized double-blind study showed that certolizumab pegol significantly improves patient-reported global response assessments of pain, urgency, and overall symptoms, and reduces the Interstitial Cystitis Symptom/Problem Index scores and pain scale score at 18 weeks. These results suggest that immunomodulatory therapy is more effective for IC/BPS patients with Hunner lesions than for IC/BPS without Hunner lesions.

Summary IC/BPS with Hunner lesions is associated specifically with immunological overreactions in the bladder; thus, immunomodulatory therapy could be a promising treatment option. Further studies focusing on the therapeutic responsiveness of IC/BPS subtypes are warranted to promote a tailored approach to clinical management of IC/BPS. To achieve this therapeutic strategy, clear and proper subtyping of IC/BPS is mandatory.

Keywords Interstitial cystitis · Bladder pain syndrome · IC/BPS · Painful bladder syndrome · Autoimmune cystitis · Immunomodulating therapy

Abbreviations

BPS	Bladder pain syndrome
ESSIC	International Society for the Study of IC/BPS
GRA	Global response assessment
IC	Interstitial cystitis
ICSI	Interstitial Cystitis Symptom Index
ICPI	Interstitial Cystitis Problem Index
VAS	Visual analogue scale

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Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic debilitating syndrome characterized by chronic urological pelvic pain in conjunction with lower urinary tract symptoms. IC/BPS encompasses a diverse variety of clinical phenotypes with different potential etiologies [1]. In this syndrome complex, IC/BPS with Hunner lesions is a clinically relevant subtype that has distinct features with respect to histology, gene expression, and clinical prognosis when compared with other forms of IC/BPS [2]. Recent evidence shows that IC/BPS with Hunner lesions is a robust inflammatory disorder characterized by enhanced immune responses, while IC/BPS without Hunner lesions may be a non-inflammatory disorder with little histological changes in the bladder; the latter may potentially be associated with systemic neurophysiological dysfunction [2]. Thus, the etiologies of IC/BPS with and without Hunner

lesions are totally different and these two subtypes should be treated separately in terms of clinical management. In this article, we review the proper categorization of IC/BPS based on recent basic evidence and discuss the potential role of immunomodulatory therapies for the treatment of IC/BPS, particularly for IC/BPS with Hunner lesions.

Pathophysiology and Classification of IC/BPS

Currently, IC/BPS is categorized into two subtypes according to the cystoscopic presence or absence of Hunner lesions: IC/BPS with Hunner lesions (also known as the International Society for the Study of BPS (ESSIC) BPS type 3) and IC/BPS without Hunner lesions (which includes ESSIC BPS types 1 and 2) [3]. Past studies demonstrate that these two subtypes cannot be differentiated by clinical phenotyping [4••]; however, IC/BPS with Hunner lesions is characterized clinically by older age at disease onset, more severe bladder-centric symptoms (including bladder/urethral pain and lower urinary tract dysfunction), reduced bladder capacity, fewer comorbid systemic conditions, and more favorable responsiveness to endoscopic treatments [5•, 6]. This bladder-centric nature of IC/BPS with Hunner lesions is also supported by proven bladder histology [7]. Bladders affected by this subtype manifest epithelial denudation and chronic inflammatory changes such as lymphoplasmacytic and mast cell infiltration, stromal fibrosis, and edema, which result in mucosal injury. We found that the accumulation of plasma cells and frequent expansion of light chain–restricted B cells are the characteristic inflammation properties of IC/BPS with Hunner lesions [8••]. In addition, studies have identified deposits of immunoglobulin and complement, along with an increased expression of chemokine receptor CXCR3 and its ligands (CXCL9, 10, and 11), in the bladder tissue of patients with IC/BPS with Hunner lesions [9–11]. These findings suggest that immunological inflammatory processes may underlie the pathophysiology of IC/BPS with Hunner lesions. By contrast, IC/BPS without Hunner lesions is characterized by bladder-beyond clinical symptoms that may be due to the other common systemic pain conditions and psychosocial health problems [12••]. Recent studies suggest that the underlying biological processes responsible for the symptoms of IC/BPS without Hunner lesions could be linked to those of widely known somatoform disorders or functional somatic syndromes such as irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and migraines, where neurophysiological dysfunction may underlie the pathogenesis [13]. In fact, bladders of patients with IC/BPS without Hunner lesions show few histological changes [8•]. Another potential pathophysiology of IC/BPS without Hunner lesions is the urothelial malfunction that contributes to the disrupted barrier function [14–16]. Urothelial alterations such as dysregulated tight junctions, structural defects, or degenerative changes impair barrier function, resulting in increased permeability and persistent afferent nerve stimulation and subsequent central nerve sensitization with subtle bladder insults [17]. Collectively, this evidence strongly suggests that IC/BPS without Hunner lesions is a non-inflammatory disorder, potentially associated with neurophysiological dysfunction. A recent whole transcriptome analysis of IC/BPS by next-generation RNA sequencing supports this concept; this study demonstrates that genes involved in immunological inflammation are upregulated in the bladders of patients with IC/BPS with Hunner lesions, while no significantly altered genes and biological pathways were found in patients with IC/BPS without Hunner lesions compared with non-inflamed controls [18••].

Glomerulations (mucosal bleeding after bladder overdistension) are another characteristic disease marker of IC/BPS; these are thought to reflect abnormal angiogenesis in IC/BPS [19]. However, recent studies show that glomerulations do not affect gene expression, nor do they reflect subepithelial inflammatory changes and neovascularization, suggesting that they may not be a phenotypic feature of IC/BPS [18••, 20••]. Likewise, mast cell infiltration, which is generally accompanied by inflammatory reactions, is considered to be one of the histological characteristic features of IC/BPS [21]. However, recent studies demonstrate that elevated mast cell infiltration is not a characteristic of IC/BPS, and equivalent mast cell density can be observed between IC/BPS and non-IC controls [22, 23].

Taken together, IC/BPS with Hunner lesions should be recognized as an independent chronic immunological inflammatory disease, while the remaining forms that lack Hunner lesions should be regarded as non-inflammatory conditions. This concept mandates that immunomodulatory therapies should be implemented in patients with Hunner lesions rather than in those without Hunner lesions.

Current Immunomodulatory Therapies for IC/BPS

Steroids

Steroid therapy is used for a wide range of conditions caused by dysregulated immune responses, including allergic reactions. Steroids exert anti-inflammatory and immunosuppressive effects by binding to glucocorticoid receptors (GCRs), which regulate transcription factors such as nuclear factor kB (NF-kB)/activator protein 1 (AP-1) (genomic effects), or by rapid interaction with the membrane-bound and/or cytosolic GCRs (nongenomic effects), resulting in increased expression of anti-inflammatory and regulatory proteins such as IL-10 and IkB, suppression of synthesis of proinflammatory proteins such as IL-2, tumor necrosis factor (TNF), and

interferon-γ, or inhibition of T cell activation [24]. A prospective trial of 14 patients with IC/BPS with Hunner lesions demonstrated that 25 mg of oral prednisone reduced the total score for the O'Leary index by 22% and improved pain management by 69% over a mean follow-up period of 16.7 months (range, 1–39) [25]. By contrast, a prospective analysis of 30 patients with IC/BPS with Hunner lesions reported that intravesical submucosal injection of triamcinolone at the sites of Hunner lesions reduced the International Prostate Symptom Score and the Pelvic Pain and Urgency/Frequency Symptom Scale significantly, with 21 (70%) patients reported as "very much improved" in the Patient Global Impression of Change assessment at 4 weeks post-injection [26]. Another retrospective study reported that submucosal injection of triamcinolone at sites of Hunner lesions caused a significant reduction in the visual analogue scale (VAS) for pain scale score in 20 patients with IC/BPS with Hunner lesions over a median follow-up of 7 months (range, 1–15); however, repeat injections were required by eight patients over the study period due to the temporary nature of efficacy [27]. The current IC/BPS guidelines do not recommend proactive steroid therapy due to the poor risk-benefit ratio (adverse effects can include osteoporosis, diabetes mellitus, myopathy, and hypertension) [28]. However, as long as it is applied only to patients with Hunner lesions (and the presence of chronic inflammation is confirmed histologically), steroid therapy is an attractive treatment option due to its powerful and cost-effective properties. Future placebo-controlled prospective studies in which IC/BPS subtypes of the cohort subjects are definitively categorized should be mandatory to ensure better clinical implementation of steroid therapy in those with IC/BPS.

Cyclosporine A (CyA)

CyA suppresses the activation of T cells by inhibiting the enzymatic activity of calcineurin [29]. CyA is used widely as an immunosuppressive drug to treat those with organ transplants and autoimmune diseases. A prospective study of CyA therapy in 11 patients with IC/BPS demonstrated that treatment for 3–6 months led to a significant decrease in voiding frequency, and an increase in the mean and maximum voided volumes [30]. A subsequent retrospective analysis from the same group confirmed the long-term efficacy of CyA treatment in 23 patients with IC/BPS, reporting significant changes in voiding frequency (from 20.8 ± 6.8 to 10.2 ± 3.8/day, $p < 0.001$) and maximum voided volume (from 161.8 ± 74.6 to 360.7 ± 99.3 mL, $p < 0.001$) after 1 year; the effects lasted through the follow-up period (mean, 60.8 months) [31]. A randomized clinical trial of CyA versus pentosan polysulfate sodium (PPS) showed the superiority of CyA over PPS, with a 75% versus 19% clinical response rate (based on a patient-reported global response assessment [GRA]) for CyA versus PPS, respectively. After 6 months of treatment, patients treated with CyA showed significant clinical improvement compared with those treated with PPS with respect to changes in 24-h urinary frequency (− 6.7 ± 4.7 vs. − 2.0 ± 5.1, $p < 0.001$), nocturia (− 2.2 ± 1.6 vs. − 0.2 ± 2.1, $p < 0.001$), O'Leary-Sant Interstitial Cystitis Symptom/Problem Index (ICSI/ICPI) scores (− 7.9 ± 4.6/− 7.1 ± 4.4 vs. − 2.0 ± 2.6/− 1.5 ± 1.8, $p < 0.001$), VAS for pain scale score (− 4.7 ± 3.5 vs. − 1.6 ± 3.3, $p < 0.001$), maximum bladder capacity (81 ± 94 mL vs. 2.8 ± 60, $p = 0.003$), and mean voided volume (59 ± 57 mL vs. 1 ± 31, $p < 0.001$), respectively [32••]. Past retrospective studies suggest that there might be differences in CyA treatment responses between subtypes of IC/BPS. Forrest et al. [33••] reported that CyA is more effective for patients with Hunner lesions than for those without; 29 of 34 patients (85%) with Hunner lesions responded to CyA treatment (defined as marked improvement on the 7-graded GRA or as a 50% reduction in the ICSI score), while only 3 of 10 (30%) patients without Hunner lesions responded. Likewise, Crescenze et al. [34] reported the superiority of the Hunner lesion subtype with respect to the efficacy of CyA treatment in an open-label study of 26 refractory patients with IC/BPS; 75% (3/4) of responders had Hunner lesions. They also reported that monitoring drug levels at 2 h after the morning dose, rather than trough levels, allowed dose reductions and minimized toxicity (e.g., hypertension or renal dysfunction). Taken together, CyA treatment has the potential to become a crucial treatment option for refractory IC/BPS patients with Hunner lesions. During CyA treatment, careful observation of possible adverse events such as increased serum creatinine levels, hypertension, alopecia, gingival hyperplasia, transient tremors, and growth of facial hair is mandatory. A randomized, placebo-controlled, multicenter, larger prospective trial of CyA treatment for IC/BPS, with clear subtyping, is warranted to validate its potential as a promising therapeutic option.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) exerts immunosuppressive effects by inhibiting the proliferation of T and B lymphocytes. MMF is used widely to treat patients after transplantation or patients with inflammatory and autoimmune disorders such as inflammatory uveitis, systemic lupus erythematosus, or lupus nephritis. A randomized, double-blind, placebo-controlled, multicenter clinical trial was undertaken to investigate the efficacy of MMF on refractory IC/BPS; however, it had to be abandoned due to the risk of fatal harm during pregnancy [35]. However, an interim analysis could not confirm that MMF was more effective for IC/BPS than placebo (response rate based on GRA: 15% vs. 16%, respectively) [35]. Like for other potential immunomodulatory therapies, a randomized, placebo-controlled, large prospective trial of MMF for refractory IC/BPS is needed under the definitive distinction of patients' subtypes.

Tacrolimus

Tacrolimus hydrate is another calcineurin inhibitor isolated from *Streptomyces tsukubaensis*. The drug interferes with the transcription of the IL-2 gene and suppresses the mixed lymphocyte reaction. The immunosuppressive activity of tacrolimus surpasses that of CyA [36]. Although a number of clinical studies have been performed for other conditions with positive results, few clinical trials of tacrolimus have been conducted for IC/BPS. A case report shows the benefit of combined tacrolimus and prednisolone on urinary symptoms in a patient with IC/BPS; this patient was refractory to conventional treatments such as hydrodistention, tricyclic antidepressants, or antihistamine. Combination therapy comprising tacrolimus and prednisolone reduced voiding frequency from 60 to 15 times per day, with pelvic pain disappearing [37]. Another case report confirmed the same effects of tacrolimus/prednisolone in an IC/BPS patient with Hunner lesions and comorbid primary Sjögren's syndrome [38]. In that report, combination therapy with tacrolimus/prednisolone increased the mean (from 85 to 263 mL) and maximum (from 120 to 400 mL) voided volume and the maximum urinary flow rate (from 11 to 31 mL/s), decreased urinary frequency (from 17.5 to 9.5 per day), reduced the ICSI/ICPI scores (from 14 to 2, and 11 to 2, respectively), and reduced the VAS for pain scale score (from 7 to 3). The efficacy of combination therapy was sustained for more than 2 years with a maintenance dose of both agents. Future clinical trials are awaited to investigate the potential efficacy of tacrolimus for the treatment of IC/BPS.

Anti-TNFα Monoclonal Antibody

TNFα is a key inflammatory cytokine produced by macrophages, T lymphocytes, NK cells, and mast cells. TNFα mediates anti-infective/anti-tumor effects by increasing expression of cell adhesion molecules, inducing cell apoptosis, and upregulating the production of antibodies and inflammatory mediators such as interleukin-1, interleukin-6, and prostaglandins, ultimately resulting in stronger immune responses. Increased levels of TNFα have been reported in various immune-related and inflammatory conditions, and TNFα monoclonal antibodies have been used to treat conditions such as rheumatoid arthritis, psoriasis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis. With respect to IC/BPS, we used next-generation RNA sequencing of bladder mucosal biopsies to show that the TNFα signaling pathway was significantly enhanced in IC/BPS with Hunner lesions compared with IC/BPS without Hunner lesions and non-IC/BPS controls [18••]. In a rat cystitis model, local blockade of TNFα ameliorated pelvic pain behavior and bladder overactivity [39]. These findings suggest the potential utility of blocking TNFα for the treatment of IC/BPS with Hunner lesions. Recently, Bosch conducted a randomized, double-blind, placebo-controlled trial of certolizumab pegol, a novel anti-TNFα monoclonal antibody, in patients with refractory IC/BPS [40••]. At week 18, certolizumab pegol (administered at weeks 0, 2, 4, and 8) significantly improved the GRA for pain, urgency, and overall symptoms ($p = 0.002$, 0.02, and 0.006, respectively) compared with placebo. Certolizumab pegol improved the ICSI/ICPI scores (− 3.6 [$p = 0.03$] and − 3.0 [$p = 0.042$], respectively), and 11-point numerical pain (− 2.0, $p = 0.02$) and urgency (− 1.7, $p = 0.03$) scale scores significantly from baseline at week 18 (compared with placebo). In this trial, the efficacy of certolizumab pegol against each subtype of IC/BPS (with or without Hunner lesions) was not clarified since cystoscopic subtyping was not performed at the time of enrollment. However, given the robust chronic inflammatory nature of IC/BPS with Hunner lesions, the certolizumab pegol arms in this study might have included higher numbers of patients with Hunner lesions than those in the placebo arms. Further clinical trials that clearly differentiate the subtype of IC/BPS within the cohort should be carried out to validate the possible efficacy of certolizumab pegol for the treatment of IC/BPS.

Other Immunomodulatory Drugs with Potential Efficacy for IC/BPS

CD20 Monoclonal Antibody

Rituximab, a chimeric CD20 monoclonal antibody, is used widely to treat autoimmune diseases and certain types of blood cancers characterized by B lymphocyte–dominant cell infiltration and/or associated abnormalities [41]. We showed previously that the inflammatory properties of IC/BPS with Hunner lesions are characterized by B cell abnormalities, including predominant B cell infiltration with frequent clonal expansion [8•]. This evidence implies the potential utility of B cell depletion therapy for the treatment of IC/BPS with Hunner lesions. Future pre-clinical studies that explore the effects of Rituximab in animal models of experimental autoimmune cystitis may be needed.

Anti-B Cell Activating Factor Monoclonal Antibody

Belimumab is a human monoclonal antibody specific for B cell–activating factor, which is required for the survival and activation of B cells [42]. Belimumab has been proven safe and shows modest efficacy in patients with systemic lupus erythematosus or Sjögren's syndrome [43, 44]. Given the above-mentioned underlying B cell abnormalities in IC/BPS with Hunner lesions, Belimumab may have therapeutic potential for the treatment of IC/BPS with Hunner lesions.

Conclusions and Future Perspectives

Recent evidence has changed the perception of IC/BPS. IC/BPS with Hunner lesions is a distinct inflammatory disease potentially associated with increased immune responses. Meanwhile, IC/BPS without Hunner lesions is almost certainly a non-inflammatory disorder (with few histological changes) that is often associated with systemic hypersensitivity and, potentially, shares underlying biological processes with other neurophysiological/endocrine abnormalities. This evidence suggests that IC/BPS with and without Hunner lesions should be seen as totally different disease entities and therefore regarded separately in both clinical practice and basic studies. Based on this concept, immunomodulatory therapies should be used to treat patients with IC/BPS with Hunner lesions while paying careful attention to adverse effects; such treatments have great potential for helping those with IC/BPS with Hunner lesions. Proper and clear subtyping of IC/BPS is necessary to achieve better clinical management and research progress.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been published previously and comply with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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