Therapeutic Strategies for Interstitial Cystitis

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INTRODUCTION

Interstitial cystitis (IC) is characterized by bladder pain associated with urgency, frequency, nocturia and sterile urine. The diagnosis of IC is based on symptomatology and urological findings, including characteristic cystoscopic features after hydrodistention under anesthesia [1]. IC has been classified into classic and non-ulcer types based on cystoscopic findings [2]. Classic IC, also called Hunner's ulcer, is found in 5%-20% of IC patients and is characterized by observable bladder ulcerations after hydrodilatation [3]. Non-ulcer IC, also called early IC, is characterized by glomerulation and petechiae formation after hydrodilatation under anesthesia. Although many pathogeneses of IC have been proposed, the actual etiology remains unclear [4].

Although enthusiastic research has been performed over several decades, the actual pathophysiology of IC and treatment for this disease of mystery remain indefinite. Recent investigations have gradually explored the possible pathogenesis of this disease and the therapies targeting each possible underlying pathophysiology are emerging. Possible etiologies include: (1) a post-infection autoimmune process, (2) mast cell activation induced by inflammation, toxins or stress, (3) urothelial dysfunction and increased permeability of the urothelium, (4) neurogenic inflammation resulting in serial reactions including potassium ion diffusion, mast cell activation, up-regulation of sensory fibers, release of neuropeptide (substance P) and bladder pain.

There is increasing evidence for the role of neurogenic inflammation in the pathophysiology of several diseases, including asthma, arthritis, migraine and, possibly, IC [5]. Preliminary studies have shown an increase in levels of immunoreactive substance P and nerve growth factor in the bladder tissue and urine [6,7]. The primary nerves involved in neurogenic inflammation are thought to be mainly C-fibers, although A- δ fibers also play a role. Recently, $P2X_3$ deficient mice have been shown to have hyporeflexic bladders and reduced pain-related behavior, indicating that $P2X_3$ is critical for peripheral pain responses and afferent pathways controlling urinary bladder volume reflexes [8]. The $P2X_3$ receptors have also been shown to localize on the suburothelial C-fibers and detrusor muscles, and co-localize with other sensory receptors, such as TRPV1, NK1, CGRP, trkA and other sensory-related receptors [9]. Any insult to the urothelium or directly to the bladder wall may induce a cascade of inflammatory reactions and produce painful inflammation, such as in IC [10].

From the above evidence, it is possible to postulate that IC syndrome might be induced sequentially by:

1. Level 1: Urothelium injury: such as in acute bacterial cystitis, intravesical foreign body, intravesical instrumentation and surgical bladder trauma.
2. Level 2: Suburothelial inflammation from urothelium, endogenous toxin or allergic reaction.
3. Level 3: Chronic inflammatory cell infiltration in the suburothelium and detrusor after the acute reaction.
4. Level 4: Chronic scar formation in the suburothelium and detrusor.
5. Level 5: Increased inflammatory reaction in the dorsal horn ganglia and corresponding sacral cord.

It is possible that IC is a progressive disease that evolves from early stage to late stage conditions. Insult to the visceral organ initiates an inflammatory process in the organ. The inflammatory reaction will proceed along the sensory nerves in the dorsal horn ganglion as well as the sacral cord. The sensory impulse will also ascend to the corresponding cortical gyrus. Therefore, any injury or inflammation in the urinary bladder will not only activate an inflammatory process in the bladder wall but also in the sacral cord and cerebral cortex. Patients might have early inflammatory reaction and produce characteristic IC symptoms, including bladder pain, urgency, frequency and positive KCl test. If the insult does not continue, the defense mechanism will solve the inflammation and patients may have symptom relief after symptomatic treatment. However, if the bladder insult continues, the inflammatory reaction will be raised to a higher level and cause permanent inflammation printing. Some patients with chronic IC might have referred pain due to the presence of high level inflammation. The following review is a list of therapies targeting different levels of neurogenic inflammation in chronic IC.

TARGETING UROTHELIAL DYSFUNCTION

Oral Pentosan Polysulphate (PPS)

More than 50% improvement in frequency, nocturia, urgency and pain has been achieved in IC patients treated with 300-400 mg of PPS per day for 4 months [6]. The response to treatment was not dose-dependent and the duration of therapy appeared to be more important than the dose [11].

Cystoprotek®

Cystoprotek® was formulated with natural glycosaminoglycan (GAG) components chondroitin sulfate and sodium hyaluronate to provide urothelial protection. In a non-controlled study, Cystoprotek® was found to be effective in 37 patients with IC [12].

Intravesical heparin therapy

A total of 56% of patients had improvement in a 3-day voiding diary and cystometrograms after intravesical 10000 U heparin therapy for 3 months [13]. Kuo treated 40 IC patients who had a positive KCl test with intravesical heparin 25000 IU retained for 2 hours, twice per week for 3 months. The symptom scores of 29 (72.5%) patients improved by > 50%. Urodynamic study revealed significant improvement in the first sensation of filling and bladder capacity after heparin treat-

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ment [14]. A combination of 4000 U heparin and 3 mL alkalinized lidocaine has recently been used to treat IC patients with a reported good effect [15].

Intravesical hyaluronic acid

Hyaluronic acid is a non-sulfated mucopolysaccharide component of the GAG layer and is believed to be present in subepithelial connective tissue to protect the bladder wall from irritants in the urine. Intravesical treatment with this agent has been investigated in IC patients. Morales et al treated 25 IC patients refractory to any treatment with 40 mg hyaluronic acid weekly for 4 weeks and then monthly. They found an initial 56% positive response rate at week 4 and a 71% positive response rate at week 12. The response was maintained until week 20 but decreased after week 24 [16]. A recent prospective, non-randomized study, with a 3-year follow-up, of 20 IC patients revealed subjective continuing improvement in pain and frequency, with 55% of patients treated with intravesical hyaluronic acid choosing to continue treatment for symptomatic relief [17].

Intravesical chondroitin sulphate

Chondroitin sulphate is a major component of the GAG layer and comprises 1/3 of the total proteoglycans on the bladder surface. Thirteen of the 18 IC patients treated (66.7%) reported improvement in lower urinary tract symptoms [18].

Intravesical PPS treatment

Bade et al treated 10 IC patients with 300 mg PPS in 50 mL 0.9% saline twice a week for 3 months and 10 patients with a placebo. Four of the treated patients and 2 control patients had significant symptomatic relief. Eight continued PPS therapy and 4 without treatment had symptomatic relief [19].

TARGETING ACUTE SUBUROTHELIAL INFLAMMATION

Antihistamines

The activation of mast cells in the bladder wall has been postulated to play an important role in the pathogenesis of IC, especially in bladder pain symptoms [20]. However, a recent study conducted by the IC Clinical Trial Group (ICCTG) revealed no significant difference in clinical efficacy between hydroxyzine and PPS [21].

Amitriptyline

Amitriptyline is a tricyclic antidepressant with central and peripheral anticholinergic effects. It has antihistamine sedation effects, and inhibits serotonin and norepinephrine reuptake. Hanno et al first reported a 95% improvement in bladder pain and daytime frequency after treatment with amitriptyline [22]. In a recent double-blind, controlled study, van Ophoven et al found a response rate of 64% in 94 patients treated with amitriptyline 12.5-150 mg (mean 55 mg) for 6 weeks [23].

TARGETING CHRONIC SUBUROTHELIAL INFLAMMATION

Bladder hydrodistention

For intravesical treatment of IC, hydrodistention of the bladder is the first choice for diagnosis, biopsy and treatment. Although hydrodistention is effective for relief of IC bladder symptoms, the symptoms usually recur within 2 weeks and repeat hydrodistention is necessary. Prolonged hydrodistention under epidural anesthesia with an intravesical pressure equal to the mean arterial pressure of the patient has been shown to give long-term effects [24,25].

Corticotherapy

Soucy et al treated 14 patients with ulcerative IC refractory to first line therapies. Among the 9 patients who continued to use prednisolone, the overall results showed a 22% reduction in symptom scores and 69% improvement in pain [26].

Cyclosporine A

Sairanen et al found that cyclosporine A 1.5 mg/kg bid was superior to PPS 100 mg tid in all clinical outcome parameters measured at 6 months. The clinical response rate was 75% for the cyclosporine A group compared to 19% for the PPS group [27].

Intravesical Dimethylsulphoxide (DMSO) treatment

DMSO provides an anti-inflammatory effect, analgesia, muscle relaxation and alteration of the collagen response, and has an influence on conduction and neurotransmission in sensory nerves. Relief of symptoms was reported in 50% of IC patients treated with 50 mL of 50% DMSO retained for 15-20 minutes, given once a week for 2-3 months. However, the relapse rate was 35%-40% over a 24 month follow-up [28].

Intravesical Bacillus Calmette-Guerin (BCG) treatment

The use of BCG in the treatment of IC aims to modulate immunological and allergic responses in the IC bladder wall [29]. In long-term follow-up, 89% of patients who responded favorably after 6 weeks BCG treatment continued to have an excellent response at 24-33 months [30]. However, the ICCTG recently reported the results of a multi-center, randomized, double-blind, placebo-controlled trial of intravesical BCG, and the response rate was 12% for the placebo and 21% for BCG ($p=0.062$). Intravesical BCG treatment was considered ineffective in the treatment of refractory IC [31].

Intravesical vanilloids

Vanilloid receptors (VR1) have been found to locate on the urothelial cells, suburothelial sensory afferents and smooth muscle cells. VR1 co-localizes with $P2X_3$ receptors, mediating stretch, pain and noxious stimuli. Desensitization of VR1 receptors may deplete terminal nerve endings and end pain [9,32]. Lazzeri et al treated 18 IC patients with single doses of 10 nM resiniferatoxin (RTX) or a placebo. Significant improvements in frequency, nocturia and pain scores were noted at 30 days but the therapeutic effects were reduced at 3 months [33]. In a preliminary study, Kuo found multiple intravesical treatments with RTX 10 nM once a week for 4 weeks was well tolerated, and reduced bladder pain and increased the symptom score in 58% of 12 women with chronic IC [34]. A recently reported multi-center, randomized, placebo-controlled trial to assess the efficacy and safety of single-dose resiniferatoxin to treat IC revealed no significant difference between resiniferatoxin and a placebo [35].

TARGETING SCARRING OF THE SUBUROTHELIUM AND DETRUSOR

Intravesical botulinum toxin A (Botox)

Botox is an inhibitor of acetylcholine release at the presynaptic neuromuscular junction. Inhibition of acetylcholine release results in regional decreased muscle contractility at the injection sites. A significant decrease was noted in $P2X_3$ immunoreactivity of suburothelial fibers at 4 weeks, with a further decrease at 16 weeks, after Botox injection in the responders of detrusor overactivity [36]. The study speculated that Botox might reduce production/uptake of neurotrophic factors and regulate expression of VR1 and/or $P2X_3$. In an animal model, Chuang et al found that intravesical Botox blocked acetic acid induced bladder pain responses and inhibited CGRP release from afferent nerve terminals [37]. Smith et al treated 13 IC patients and concluded that Botox might have an antinociceptive effect on bladder afferent pathways in IC patients [38]. In another study, Kuo used suburothelial injections of Botox to treat 10 women with IC and improved results were reported in 7. All patients with therapeutic effects had dysuria after treatment [39]. The effect of Botox on IC patients was further confirmed by a recent study in which Giannantoni et al treated 14 patients with injections of 200 U of Botox in 20 mL saline at 20 sites in the trigone and bladder base. Twelve patients (85.7%) reported subjective improvement at 1 and 3 months [40].

TARGETING DORSAL ROOT GANGLIA (DRG) AND SACRAL CORD INFLAMMATION

There is no evidence-based therapy for treatment of sacral cord inflammation in chronic IC. Intravesical Botox injections not only reduce bladder sensitivity in IC patients but also induce desensitization in the central nervous system by affecting the over-expression of activated proteins in the dorsal horn ganglia [41]. Through repeat intravesical Botox injections, desensitization of the inflammation in the dorsal horn ganglia or sacral cord might be gradually diminished.

MULTIMODAL THERAPY FOR IC

Since the etiology of IC is thought to be multi-factorial, multiple therapies might produce synergistic effects and better outcomes. In treating chronic IC, it is crucial to identify the level of neurogenic inflammation in individual patients and institute appropriate therapy. In a patient with high level inflammation, combination therapy may be necessary in order to treat high level inflammation and to prevent the continuing bladder insult, such as urothelial dysfunction. The principles for treatment of IC are based on: (1) controlling the dysfunctional epithelium by continual replenishment of the GAG layer, (2) inhibiting neurological hyperactivity by administration of amitriptyline or imipramine, (3) suppression of allergies with antihistamines, and (4) pain control with non-steroid anti-inflammatory drugs (NSAIDs), Cox-2 inhibitors or tranquilizers.

Non-pharmacological approaches, such as bladder training, biofeedback and dietary changes, can also provide supplementary relief and should be added to the treatment of refractory IC [42]. For patients who are refractory to oral medication or intravesical instillation therapy, intravesical injections of Botox might provide a chance for symptomatic relief.

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