ELSEVIER

IMMUNOMODULATORS FOR TREATMENT OF INTERSTITIAL CYSTITIS

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Interstitial cystitis (IC) is a disorder of the urinary bladder characterized by urgency, frequency, nocturia, and chronic pelvic pain. The main pathologic findings include dysfunction of the bladder glycosaminoglycan protective layer[1] and a high number of activated bladder mast cells[2]; these processes could lead to neurogenic inflammation and immune damage of the bladder wall, with subsequent chronic nerve sensitization[3] (Fig. 1). As IC has become better known and the diagnostic criteria presently do not necessarily include cystoscopy, it has been estimated that 1 million women in the United States have IC.[4] Many patients with IC also have allergies, fibromyalgia, and irritable bowel syndrome,[5] all of which are exacerbated by physical or emotional stress.[6,7] In fact, a recent publication has linked IC and panic disorder genetically, and it is of interest that benzodiazepines, which are used in the treatment of panic disorder, can bind to mast cells, leading to inhibition of serotonin release.[8]

Despite almost 20 years of research, approved treatments for IC are limited to intravesical administration of dimethylsulfoxide (Rimso) and oral pentosanpolysulfate (Elmiron)[9]; recent findings, however, have challenged their universal effectiveness.[10] In view of the above and because IC pathogenesis appears to be multifactorial,[11,12] the treatment of IC is particularly challenging. Treatment should, therefore, use a multimodal approach, especially with immunomodulators, which have not received sufficient attention to date. We discuss a number of oral or parenteral compounds in alphabetical order of the single or key active ingredient. Trade names are provided in parentheses for the representative products, with additional qualification for combination products when active ingredients are listed.

Intravesical agents for IC are not covered because dimethylsulfoxide (50%), the most common drug in this category, still has an unknown mechanism of action and is no longer used often. Recent randomized, double-blind, placebo-controlled clinical trials have showed that two promising agents, bacille Calmette-Guérin (BCG)[13] and sodium hyaluronate (0.4%),[14] were not effective, although the results have not yet been published.

MAST CELL-NEURON INTERACTIONS

Patients with IC can be broadly grouped into those with bladder inflammation (a minority of whom also have Hunner's ulcers) who present with more pronounced symptoms[15] and those with minimal or no inflammation.[15] The only significant correlation between the clinical symptoms and pathologic findings reported to date has been that of nocturia and an increased number of tryptase-positive urothelial mast cells.[16] Mast cells secrete more than 12 prestored molecules, such as histamine, serotonin, proteases, and tumor necrosis factor-alpha (TNF-alpha), as well as about 20 newly synthesized mediators, such as cytokines interleukin (IL)-6, IL-8, and IL-13, which have important chemoattractant and proinflammatory actions.[2,17] In patients with IC, expression of bladder intercellular adhesion molecule-1[18] and urine levels of the proinflammatory cytokine IL-6[15,19] are increased. These findings are of particular interest because the prototypic inflammatory cytokine IL-1 can stimulate selective release of IL-6 from mast cells without degranulation, discernible only with high-power ultrastructural immunocytochemis-

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T. C. Theoharides owns CystoProtek® trademark and related patents.

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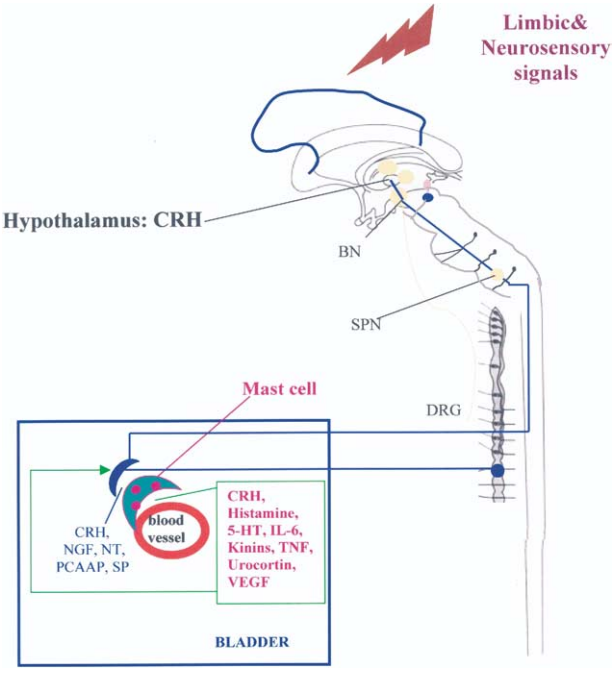

FIGURE 1. *Schematic representation of hypothesized mast cell-neuronal interactions in interstitial cystitis. Mast cell activation could occur by CRH or related neuropeptides released locally in bladder or through the pontine Barrington nucleus acting through CRH on the spinal parasympathetic nucleus that innervates the bladder. Vasoactive, proinflammatory, and nerve-sensitizing molecules released from mast cells could then further stimulate local nerve endings, propagating a pathologic loop. BN = Barrington nucleus; DRG = dorsal root ganglion; 5-HT = 5-hydroxy tryptamine, serotonin; NGF = nerve growth factor; NT = neurotensin; PCAAP = pituitary cyclic adenosine monophosphate activating peptide; SP = substance P; SPN = spinal parasympathetic nucleus; VEGF = vascular endothelial growth factor.*

try.[20] Moreover, serum IL-6 is elevated under acute stress and is entirely mast cell dependent.[21] Mast cell activation, ranging from selective release of some cytokines to full-blown degranulation with tryptase secretion, may be even more important than mast cell numbers.[7]

One of the most important concepts in the pathophysiology of IC is the activation of mast cell-neuron interactions,[22] the persistence of which, irrespective of the initiating trigger, may explain the chronicity and resistance of IC to single-modality therapy.[3] A particular aspect of such interactions is the newly discovered proinflammatory role of locally secreted corticotropin-releasing hormone (CRH) in triggering mast cell activation.[7] We recently showed that dorsal root ganglia (DRG) express large amounts of CRH and mast cells express multiple CRH receptor isoforms (unpublished data). These findings are particularly relevant because stress stimulates bladder mast cells,[23] and human mast cells are a rich source of CRH, indicating it could have autocrine actions (Fig. 1).[24]

CYCLOSPORINE (NEORAL)

Cyclosporine is a well-known immunosuppressive agent used in organ transplantation. Cyclosporine inhibits the calcium-dependent phosphatase calcineurin, which dephosphorylates a transcription factor required for IL-2 activation of T cells. Cyclosporine also inhibits allergic conditions, including mast cell activation.[25]

In one open-label study of 11 patients with intractable IC that had lasted for up to 6 months, cyclosporine (initial dose 2.5 to 5.0 mg/kg orally, followed by a daily maintenance dose of 1.5 to 3.0 mg/kg orally) reduced micturition, frequency, and bladder pain significantly in most patients.[26] However, the symptoms recurred in most patients after cessation of treatment.

ETANERCEPT (EMBREL), INFLIXIMAB (REMICADE)

Inhibition of TNF-alpha action has emerged as a powerful way to inhibit inflammation for the treatment of certain autoimmune conditions, such as rheumatoid arthritis.[27] Etanercept is a soluble human TNF receptor given subcutaneously for rheumatoid arthritis; adverse effects include headache and increased susceptibility to pulmonary infections. Infliximab is a chimeric human/mouse TNF blocking monoclonal antibody approved for intravenous treatment of rheumatoid arthritis and inflammatory bowel disease. Neither etanercept nor infliximab has so far been used in IC.

IL-10 (TENOVIL)

IL-10 is a regulatory cytokine produced mostly by T-helper-2 cells, macrophages and CD8-positive cell clones. It was originally termed "cytokine synthesis inhibiting factor" because of its ability to inhibit the production of several proinflammatory T-helper-1 cytokines from antigen-activated or mitogen-activated mononuclear cells.[28] IL-10 inhibits long-term IL-6 production and TNF-alpha release, but not preformed-mediator release from rat peritoneal mast cells.[29] Moreover, IL-10 does not inhibit tryptase and IL-6 from human leukemic mast cells.[30] Surprisingly, IL-10 exerts some immunostimulatory effects on B cells and cytotoxic T cells, possibly at higher concentrations and with a longer treatment duration.[30] Human recombinant IL-10 is currently being tested in rheumatoid arthritis, psoriasis, and inflammatory bowel disease.[28,31] Even though the results in inflammatory bowel disease have been rather disappointing because not enough cytokine reached the intestine,

the use of a gelatin microsphere containing IL-10 has been more encouraging.[31]

IMATINIB (GLEEVEC)

C-kit is a receptor that has been linked to the proliferation of a number of different cells, including mast cells. C-kit-positive cells are present in various tissues, including normal bladder cells, and IC bladder mast cells have been reported to overexpress c-kit.[32] The c-kit ligand (stem cell factor) is also chemotactic for mast cells,[33] and mast cells can also secrete stem cell factor, indicating that it could have autocrine actions.[34] C-kit mutations have been identified in patients with systemic mastocytosis.[35]

Imatinib is the first inhibitor of protein kinases, including c-kit, that was rationally designed for chronic myeloid leukemia.[36] Imatinib has also been used for systemic mastocytosis[37] and inflammatory bowel disease.[38] It would, therefore, be reasonable to investigate the effect of imatinib in at least those patients with IC who have increased bladder mast cells.

METHOTREXATE (TREXALL)

Methotrexate is a well-known folic acid synthesis inhibitor and one of the oldest chemotherapeutic agents commonly used for the treatment of certain leukemias and breast cancer. It is also used for rheumatoid arthritis and psoriasis. At low doses, adverse effects are limited to lip irritation (cheilitis), although bone marrow suppression can occur. The adverse effects can be minimized by weekly administration of folinic acid. The safety and efficacy of methotrexate was investigated in 9 women with refractory IC and led to a significant reduction in pain in about 45% of the patients, but no reduction in urinary frequency or voided volume.[39]

MONTELUKAST (SINGULAIR), ZAFIRLUKAST (ACCOLATE)

Montelukast is a leukotriene D (LTD_4)-receptor antagonist used for the maintenance of mild to moderate asthma; it is the only drug in its category used once per day.[40] As leukotrienes are implicated in allergy and inflammation, this drug could be especially useful in patients with documented bladder mastocytosis and a history of allergies and asthma. In one open-label study using montelukast (20 mg/day for 3 months) in 10 women with IC, diagnosed per the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIDDK) criteria and with at least 28 mast cells/mm^2 detrusor muscle tissue, urinary frequency, nocturia, and pain were significantly reduced.[41] Other drugs in this category are not as attractive because of their adverse effect profile; for instance, zafirlukast is another leukotriene-receptor antagonist administered twice per day, but concurrent administration increases serum concentrations of theophylline. Zileuton is an inhibitor of leukotriene synthesis, but has to be given four times per day; moreover, it is metabolized by P450 and can, therefore, increase the serum concentrations of many drugs, such as propranolol and theophylline.

SUPLATAST (IPD)

Suplatast tosilate is an antiallergic compound marketed in Japan that has been shown to inhibit IgE production from B cells and T-helper-2 cytokines, especially IL-4 and IL-13.[42] In an open-label clinical trial of 14 women that lasted 1 year, oral suplatast (300 mg/day) significantly increased the bladder capacity and reduced the symptoms of IC.[43] No significant adverse effects occurred.

QUERCETIN (CYSTAQ, CYSTOPROTEK)

Quercetin is a flavonol that belongs to the naturally occurring flavonoids found in plants and seeds.[44] Quercetin inhibits both mast cell proliferation and secretion,[44,45] especially mucosal mast cells, which are not affected by the "mast cell stabilizer" disodium cromoglycate (cromolyn).[46] A quercetin containing supplement (CystaQ, equivalent to 500 mg of quercetin twice a day for 4 weeks) used in 20 patients in an open-label clinical trial was reported to improve IC, [47] but this preparation is a proprietary formula with multiple ingredients that have not been disclosed. Proper disclosure of the contents, their source, and their purity should be an absolute requirement for all dietary supplements.[48] Quercetin has synergistic effects on mast cell inhibition[48,49] and in IC when combined (CystoProtek) with the mucosal glycosaminoglycan components sodium hyaluronate, which also reduces bladder inflammation,[50] and with chondroitin sulfate, which also inhibits mast cells.[51] An open-label study of 37 female patients with IC according to the NIDDK criteria taking six capsules per day of CystoProtek (equivalent to 900 mg of quercetin) for 6 months showed significant symptom reduction.[52] This latter preparation achieves a greater oral absorption by mixing the active ingredients with kernel olive extract; otherwise, because quercetin is very lipophilic and chondroitin sulfate is highly anionic with a very large molecular weight, their oral absorption in powder form is limited.[49]

CONCLUSIONS

The present review has attempted to indicate that mast cell-neuron interactions are a main target

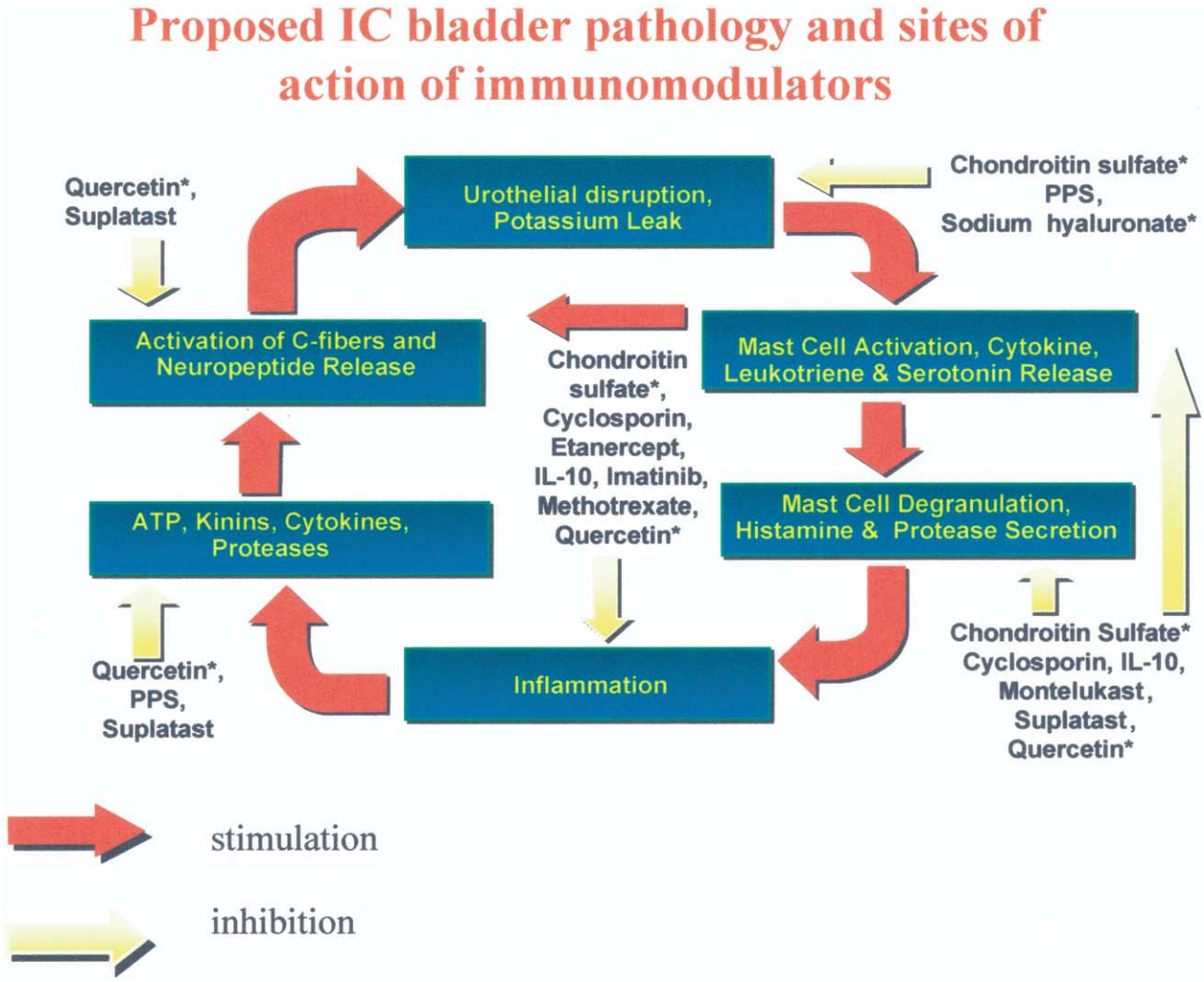

FIGURE 2. *Schematic representation of hypothesized multimodal pathophysiology of IC and proposed sites of immunomodulation listing active agents. It should be noted that single ingredients by themselves may not be sufficient; this is particularly so in the case of (*) quercetin, which is most active when combined with (*) chondroitin sulfate and (*) sodium hyaluronate in a kernel olive-extract preparation that increases their absorption (CystoProtek covered by U.S. patents 6,635,625; 6,689,748; 09/771,669 allowed August 10, 2004 and CIP of 09/056,707 filed on April 8, 1998). PPS = pentosanpolysulfate.*

for immunomodulators that could interrupt this cycle and hopefully limit progression of IC. Strategies aiming to increase therapeutic responses in IC should consider combining immunomodulating agents with other active ingredients to provide a multimodal approach (Fig. 2). Humanitarian use of select agents in intractable IC cases and clinical trials with combination products are needed. CRH receptor antagonists[53] may be useful when stress is known to worsen IC symptoms, possibly through mast cell activation.[54]

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