Chondroitin Sulfate for Interstitial Cystitis

Summary

✓ Chondroitin sulfate solution 2.0% is a glycosaminoglycan (GAG) replenishment therapy instilled into the bladder of GAG-deficient patients with interstitial cystitis (IC).

✓ Two non-randomized, uncontrolled pilot studies report improvements in patient-reported symptoms after the use of chondroitin sulfate for one year. Prospective, randomized, head-to-head trials are needed to assess the effectiveness of this technology compared with other IC therapies.

✓ The cost and demand for this technology are low, but there could be a significant impact on clinics that administer treatment, if uptake increases.

The Technology

Sterile sodium chondroitin sulfate solution 2.0% (Uracyst®, Stellar Pharmaceuticals Inc., London ON) is a GAG replenishment therapy that is instilled into the bladder of GAG-deficient patients with IC. Chondroitin sulfate is an acidic mucopolysaccharide that is one of the most prevalent components of the GAG layer in the bladder. The GAG layer prevents urinary solutes from diffusing through the bladder epithelium. GAG deficiency may be an underlying cause of IC that allows irritating urinary solutes to leak through the bladder wall into surrounding tissues. Restoration of the GAG layer by instilling products such as chondroitin sulfate are purported to bring symptomatic relief.

Regulatory Status

In Canada, Uracyst® has been approved as a Class IV medical device since July 2004, although other forms may have been available from the same manufacturer as early as 1998. The Uracyst® Test Kit contains a 100 mL pouch of sterile potassium chloride (KCl) solution 3%, and a 20 mL vial of Uracyst® to aid in the diagnosis of GAG-deficient patients.

Patient Group

IC, also known as painful bladder syndrome, is a chronic symptom complex of urinary frequency, bladder pressure, pelvic discomfort, and pain in the absence of a reasonable cause such as bacterial infection. The pathogenesis and etiology of IC are unknown. In addition to abnormal bladder epithelial permeability, other possible causes are neurogenic abnormalities, autoimmune disorders, and mast cell activation.

Because of a lack of a uniform definition, differing diagnostic criteria, and delayed time to diagnosis, IC prevalence estimates and incidence rates vary. Although the natural history of IC has not been characterized, an observational study in which IC patients were followed for up to four years suggests an initial symptom improvement due to regression to the mean (a movement over time toward "normal"), and increased follow-up and care.

A two-week Canadian urology outpatient practice audit revealed that 2.8% of the population studied were diagnosed with IC (female to male ratio of 8:1). US population-based prevalence estimates range from 0.57% to 12.6%, reflecting the uncertainty in calculating rates. Despite this, there is a consensus that IC occurs mainly in women (90%), and that the mean age at diagnosis is typically the mid-40s.

The exclusion diagnosis of IC requires an assessment of symptoms, physical examination, urine culture and sensitivity, and if indicated, urine cytology, urodynamics, or imaging (i.e., cystoscopy or laparoscopy). Patients’ diaries and symptom questionnaires may also be helpful in the management of IC.
The potassium sensitivity test (PST) may be useful for identifying GAG deficiency, although only 66% to 75% of IC patients will test positive. During the PST, which is an office-based procedure, sterile water and a KCl solution are sequentially instilled into the bladder. Afterwards, the patient rates the degree of urgency or pain produced. If painful, the PST is considered to be positive. After the PST, chondroitin sulfate is instilled to neutralize the pain, even if the result is negative. There may be a delayed reaction to the PST.

**Current Practice**

The treatment of IC is multidimensional, and often includes pharmacologic and non-pharmacologic therapies directed at symptom reduction. Initially, patient management options include dietary guidelines, bladder training, and pelvic floor physical therapy. Oral therapies include sodium pentosan polysulfate (Elmiron®, Janssen-Ortho Inc.), which is a heparin analogue, and the only oral agent indicated for the treatment of IC pain; antidepressants (e.g., amitriptyline); antihistamines (e.g., hydroxyzine); antispasmodics; non-steroidal anti-inflammatories; narcotics; and gabapentin. Bladder instillations of solutions containing dimethyl sulfoxide (DMSO, RIMSO-50), heparin, lidocaine, triamcinolone, or bacillus Calmette-Guérin (BCG) have also been used for symptomatic relief. Bladder hydrodistension may be used, but it is reported to have limited efficacy. Surgical options (e.g., sacral neuromodulation, denervation surgery, bladder augmentation, cystoplasty, or urinary diversion through cystectomy or alone) may be considered after conservative treatment has failed.

**The Evidence**

There is limited evidence about the efficacy of chondroitin sulfate for the treatment of IC. In two non-randomized, uncontrolled, open-label pilot studies of bladder-instilled chondroitin sulfate solution in IC patients that were identified, patients were required to test positive after the PST, and have their symptoms subsequently neutralized by chondroitin sulfate.

In the first trial, 18 newly diagnosed, untreated IC patients underwent chondroitin sulfate 0.2% solution instillations weekly for four weeks, then monthly thereafter for one year. Based on a per protocol analysis, patients who completed the trial used the O’Leary-Sant Interstitial Cystitis Symptom and Problem Index to rate improvement from baseline at 13 months. Six of the 13 (46.2%) completed patients rated improvement as “good,” two (15.4%) “fair,” four (30.8%) “partial,” and one (7.7%) as “none.” The average response time was three to 12 weeks. The validity and reliability of this instrument are unclear.

In the second trial, 24 patients with IC of one to 20 years duration who failed to respond to other therapies (i.e., hydrodistension, pentosan polysulfate, or anticholinergics) were treated with chondroitin sulfate 2.0% solution instillations twice weekly for two weeks, then weekly with 0.2% solution for four weeks, and monthly thereafter for one year. The average symptom improvement reported in 20 patients completing the trial was 73.1% (range 50% to 95%), although the method of measurement was unspecified. The time to optimum subjective response was four to six months, but most patients reported symptomatic improvement after three to four weeks. Eight patients needed to take the more concentrated 2.0% solution to maintain results. As a result, the use of two different doses makes interpretation of the study outcome difficult. The results should be interpreted with caution, because the validity of the responder analyses can be questioned; improvements could be due to the natural history of IC; and in the first study, there was a significant placebo effect attributed to patients’ interactions with a caring urology nurse.

A Canadian phase II-III non-randomized, uncontrolled, community-based, open-label efficacy and safety study of Uracyst® in the treatment of IC patients is underway. The primary efficacy endpoint will be the percentage of responders to a seven-point Patient Global Assessment scale at 10 weeks (i.e., after six treatments). Safety will be based on the incidence of adverse events, and the results of physical examinations and laboratory tests.
Adverse Effects

No adverse effects were reported in the published pilot studies. This is to be expected, because chondroitin sulfate is not systemically absorbed, and it does not exert any pharmacologic effect. There may be a theoretical risk of increased urinary tract infections due to the frequency of catheterizations and bladder instillations.

Administration and Cost

According to the manufacturer, Uracyst® 2.0% solution should be instilled into the bladder by catheter, and held in the bladder for a minimum of 30 minutes before voiding. This should be done weekly for four to six weeks, then monthly thereafter. The time to symptom resolution can vary, and treatment should be continued for up to one year without interruption. More frequent therapy (i.e., biweekly instillations for six weeks, and then monthly thereafter for one year) may be required in patients with severe IC.

The cost of Uracyst® is C$233.60 plus GST for a box of four 20 mL vials, and the cost of the potassium sensitivity test kit is C$64.40 plus GST (David Butts, Stellar Pharmaceutical Inc., London: personal communication, 2006 Mar 02). The cost of one year of Uracyst® solution alone could range between C$937 and C$1,062 (mild to moderate) to C$1,437 (severe) per IC patient. It is expected that instillation will be done by a health care professional in a cystoscopy or treatment clinic; the patient would pay for the solution, and possibly for the catheter. The burden on the clinics could be significant, because each patient treated would require at least one hour of clinic time, and a minimum of 15 visits annually for the mildest cases.

Concurrent Development

New treatment modalities under investigation for IC are suplatast tosilate, an immunoregulator; resiniferatoxin, a potent capsaicin analogue; botulinum toxin injections to induce paralysis; a vitamin D3 analogue, BXL 628 (BioXell), with claims of mast cell stabilization; and gene therapy to deliver analgesia to the peripheral nerves of the bladder. Recent studies of resiniferatoxin and BCG used for the treatment of IC report negative or poor outcomes.

Rate of Technology Diffusion

Although Uracyst® has been available in Canada for a few years, uptake is limited. Representatives in each province and territory were contacted to gather information about the coverage of Uracyst®. Uracyst® is ineligible for reimbursement under government-sponsored pharmacare programs, because it is classified as a medical device, not as a drug. Eight of the nine provinces that provided responses confirmed that the technology is excluded in provincial fee schedules, although there is a possibility that it is being billed under another diagnostic code or budgetary process.

Implementation Issues

It is unclear where chondroitin sulfate best fits among other treatment modalities for IC. There is limited evidence of efficacy, and because there are no controlled or head-to-head comparative trials of the technology versus an alternative therapy for IC, it is impossible to assess its relative effectiveness. Chondroitin sulfate could replace ineffective therapy, or become an add-on therapy in patients who are not achieving adequate symptom control from oral agents or other therapies. Theoretically, if patients were tested with the PST before the start of treatment, only those who are GAG deficient should receive treatment. This process could target an appropriate population of IC patients, but there is no definitive evidence for this.

The cost of and demand for chondroitin sulfate for the treatment of IC are low. There could be a significant impact on cystoscopy and treatment clinics that administer the technology, if uptake increases.

References

The Canadian Agency for Drugs and Technologies in Health (CADTH) is funded by Canadian federal, provincial and territorial governments.