

Montelukast for Symptom Control of Interstitial Cystitis

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Interstitial cystitis (IC) is a chronic disease of the bladder with an unknown etiology. This condition is commonly confused with urinary tract infections, as the symptoms are similar and include urinary urgency, frequency, and painful urination with suprapubic discomfort.¹ IC is more prevalent in females, with 60-70 cases per 100,000 females and 12-14 cases per 100,000 males in the US. Men who are affected are typically middle aged (40-60 years).² The pathogenesis of IC is poorly understood; however, several theories have been proposed and include changes in urothelial permeability, increased activity of mast cells and overproduction of leukotrienes, neural immune mechanisms, and autoimmune and infectious etiologies.³ Nonpharmacologic treatment methods include avoidance of carbonated, alcoholic, acidic, or caffeinated foods or beverages.⁴ Pharmacologic agents with Food and Drug Administration approval for the treatment of IC include oral pentosan and dimethyl sulfoxide (through intravesical installation); other treatment agents used include heparin, tricyclic antidepressants, and bacillus Calmette-Guerin. Success with these agents has been limited.^{1,5} Montelukast may be a possible or alternative treatment option for IC because of the presence of leukotriene D₄ (LTD₄) receptors on the detrusor muscle of the bladder.

This case report describes a male patient who experienced a significant decrease in IC symptoms of urinary frequency and pain with the use of montelukast.

OBJECTIVE: To describe the effects of montelukast, a leukotriene receptor antagonist commonly used in the treatment of allergic rhinitis and asthma, on the symptoms of interstitial cystitis (IC).

CASE SUMMARY: A 64-year-old male had a history of IC with previous trials of solifenacin, dutasteride, and tamsulosin and little improvement in IC symptom reduction. When montelukast 10 mg was initiated for allergic rhinitis symptoms, a substantial improvement in urinary urgency and pain during therapy was noted. This improvement subsequently disappeared when montelukast was stopped.

DISCUSSION: IC, a rare occurrence in the male population, is related to an inflammatory process and has also been associated with inappropriate leukotriene release, which is the target of montelukast therapy. In general, treatment for IC includes systemic medical therapy, local bladder treatment, surgical and neurosurgical procedures, and intravesical drug installation. Currently, montelukast is Food and Drug Administration approved for use in the treatment and prevention of mild-to-moderate asthma and exercise-induced asthma, as well as treatment of seasonal and perennial allergic rhinitis. While montelukast treatment did not cure the patient's IC, it improved his quality of life through substantial symptomatic relief, including less pain and urgency.

CONCLUSIONS: Montelukast may be an effective treatment option in the management of interstitial cystitis. Further research is needed to substantiate this novel use.

KEY WORDS: frequency, interstitial cystitis, leukotriene, montelukast, Singulair.

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Case Report

A 64-year-old white male presented to the clinic with allergic rhinitis. His history was significant for IC, Raynaud disease, asthma, hiatal hernia, benign prostatic hyperplasia (BPH), gastroesophageal reflux disease, and glaucoma. IC symptoms previously reported were frequent urination, urinary urgency, and inability to urinate without passing gas or fecal material. Previous therapies included solifenacin, dutasteride, and tamsulosin, none of which provided significant improvement in IC symptom reduction. His other medications at the time of this report included latanoprost eye drops for glaucoma and amlodipine for Raynaud disease. His social history was positive for occasional alcohol use and negative for tobacco use.

Author information provided at end of text.

To treat his allergic rhinitis symptoms the patient was started on montelukast 10 mg. Prior to treatment initiation, he reported urinating every 30 minutes. Four months after starting montelukast, he again presented to the clinic. He had been unable to fill the prescription for montelukast 1 week prior to his appointment because of financial constraints. He stated that while on montelukast, he was urinating only every 60-90 minutes. For the week prior to the appointment, while not taking montelukast, he resumed urinating every 30 minutes. He claimed that the montelukast significantly decreased pain upon urination and urgency.

Discussion

A systematic review of the literature was performed via PubMed using the key words leukotriene or Singulair or montelukast and interstitial cystitis, with publications limited to the English language and studies involving humans.

IC occurs in approximately 1.3 million Americans, 1.2 million of whom are female.⁴ IC is extremely rare in the male population. A small study of women with IC reported that after 1 month of treatment with montelukast, a significant decrease in urinary symptoms, including 24-hour urinary frequency, nighttime voiding, and pain, occurred.³ Our literature review revealed no reports of similar results in male patients. To our knowledge, this case study is the first report of a male patient with IC who experienced benefits from montelukast therapy.

The possible role of leukotrienes in IC was first described by Felsen and colleagues⁶ in 1991. An inflammatory process was suggested to be the pathogenesis behind development of IC due to the noted increase in inflammatory cells in the bladders of patients with IC. The presence of leukotrienes in the urine was noted in patients with IC, but the source of leukotriene production (bladder epithelia vs mast cells, macrophages, eosinophils, polymorphonuclear leukocytes, or basophils) was unknown.

Ten years later, studies by Bouchelouche et al.⁷ revealed the presence of LTD₄ receptors on human detrusor myocytes in the bladder. LTD₄ is a proinflammatory mediator produced with histamine from mast cells in the detrusor muscle, causing spasmogenic effects. In IC there is an increased concentration of mast cells around the detrusor muscle.⁸ Upon mast cell activation, leukotriene C₄ (LTC₄) is synthesized and released from the mast cell and converted to biologically active LTD₄ in the bladder wall. LTD₄ binding to its receptor in the bladder wall is responsible for the symptoms and pain observed in IC.⁷

The involvement of leukotrienes in inflammatory processes such as IC and their overproduction provided the basis of the study by Bouchelouche and colleagues⁹ to assess another leukotriene subtype, leukotriene E₄ (LTE₄), in the diagnosis of IC. Enzyme immunoassay was performed

using the urine of 9 healthy women and 9 patients with diagnosed IC. Mean urinary LTE₄ in healthy volunteers was 62.24 ng/mmol creatinine, while in patients with IC the average was 2.4 times greater, at 148.78 ng/mmol creatinine ($p = 0.003$). This finding further supports an increased leukotriene production in patients with IC.

The patient had previously tried solifenacin, which is an orally active antimuscarinic used in the treatment of symptoms of overactive bladder (urinary frequency, urgency, and incontinence), as IC therapy. Its mechanism of action is to decrease bladder contraction and pressure on the detrusor muscle.¹⁰ While symptoms of overactive bladder are comparable to those of IC, the pathogeneses are different, and solifenacin does not have an effect on the leukotriene release that is characteristic of IC. The patient had also tried tamsulosin and dutasteride for BPH. Tamsulosin is an α_1 -antagonist working at the level of the prostate, and it improves urinary flow in patients with bladder neck obstruction or BPH.¹⁰ This impacts urinary flow, but not urinary frequency associated with bladder muscle spasm. Dutasteride is a 5- α reductase inhibitor that is also labeled for the treatment of BPH and has an unlabeled use in the prevention of prostate cancer. Its mechanism is through inhibition of the conversion of testosterone to dihydrotestosterone (DHT), thereby diminishing DHT levels associated with prostate cancers and enlargement of the prostate.¹⁰ This, too, had an effect on urinary flow but not frequency. These treatments represent a variety of mechanisms of action to target symptom relief of IC, but until montelukast was initiated for allergic rhinitis symptoms, leukotriene overproduction and release had not been targeted.

Montelukast is an orally active compound that is indicated in the treatment and prevention of mild-to-moderate asthma and exercise-induced asthma, as well as treatment of seasonal and perennial allergic rhinitis.¹¹ The mechanism of montelukast is through inhibition of the LTD₄ receptor, which diminishes endothelial membrane permeability, airway smooth muscle contraction, and thickening of mucous secretions.¹² Although originally prescribed for allergic symptoms, montelukast provides a novel approach to the treatment of IC.

Per the manufacturer, patients receiving montelukast may experience neuropsychiatric adverse effects including agitation, suicidal ideation and behavior, hostility, aggressive behavior, hallucinations, insomnia, restlessness, anxiousness, depression, disorientation, dream abnormalities, irritability, somnambulism, and tremor.¹¹ These adverse effects should be monitored and reported to the physician. The patient in this case had no complaints of these adverse reactions while on the montelukast therapy.

To our knowledge, this is the first case report of a male responding to or reporting improvement in IC symptoms with montelukast. Montelukast antagonizes LTD₄ receptors in the bladder wall that are responsible for the spasmogenic

effects on the detrusor muscle of the bladder in IC. Our case study shows that it is possible that montelukast can be used as a treatment option to reduce IC symptoms of urgency, frequency, and pain, and improve patient quality of life in males in addition to females. Further research is needed to substantiate this novel use.

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