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ROLE OF LEUKOTRIENE RECEPTOR ANTAGONIST MONTELUKAST IN THE TREATMENT OF CHRONIC URTICARIA: A HOSPITAL BASED STUDY

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Abstract
Introduction: Chronic urticaria is a disabling disease which may be refractory to standard therapies. Leukotriene receptor antagonists like montelukast have been tried in allergic diseases like asthma and find mention as a therapeutic option in chronic urticaria.
Purposes: A randomized single-blinded non-placebo controlled study to evaluate the role of montelukast, in addition to the adjunctive role of non-sedating antihistamine levocetirizine (H1), was conducted in patients with chronic urticaria.
Methods: Thirty-five patients with chronic urticaria were enrolled. Medication was given for a period of twelve weeks. Montelukast 10mg/day in an adult and 5mg in the age group 6-13 years, 4mg 2-6 years and levocetirizine 5mg once a day was added, if patient had new weals while on therapy. The improvement was monitored by estimating the episodes of wheals and pruritus in any two weeks period.
Results: Twenty-two patients showed a good response with occasional wheals at the end of 2 weeks and no weals at the end of 12 weeks. These included all 8 patients on non-steroidal anti-inflammatory drugs (NSAIDS). Four of these patients relapsed on discontinuation of therapy.
Conclusions: Montelukast is effective in chronic refractory urticaria especially in patients on non-steroidal anti-inflammatory drugs with occasional add-on use of a non-sedating anti-histamine.

Key words: chronic urticaria; montelukast; levocetirizine

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Introduction

Chronic urticaria is a disabling condition in which recurrent pruritic weals manifest on the body daily or for most days of the week for longer than 6 weeks. Pathophysiologically it is characterized by local vasodilatation and increased permeability of capillaries and small venules followed by transudation of plasma constituents into the papillary and upper reticular dermis. A large number of substances including kinins, prostaglandins, leukotrienes, proteolytic enzymes and the best-known histamine have been found to elicit the typical weal and flare reactions [1-4].

Anti-histamines are the first-line treatment for all patients with chronic urticaria. Chronic urticaria may however often be refractory to standard therapy. For patients with severe, unremitting urticaria who have failed to benefit from conventional therapies, other modalities have been tried. As urticaria symptoms can have a profound effect on a patient's quality of life (QoL) therefore treatment should address both relief of physical symptom and improvements in QoL. One such class of drugs is the leukotriene receptor antagonists (LTRA). Leukotrienes are derived from arachidonic acid, a constituent of the membrane phospholipid bilayer, and are produced by inflammatory cells (neutrophils, eosinophils, mast cells/basophils, monocytes/macrophages and lymphocytes). Much is known about the role of leukotrienes in asthma and allergic rhinitis. Leukotrienes promote microvascular leakage, airway mucus secretion and airway edema. Montelukast blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in the lungs. Leukotriene receptor antagonists like montelukast have been tried in chronic urticaria with variable results. A randomized single blinded non-placebo controlled study to evaluate the role of montelukast in addition to the adjunctive role of non-sedating antihistamine levocetirizine (H1) was conducted in patients with chronic urticaria [5-7].

Material and Methods

Thirty-five patients with chronic urticaria who attended the outpatient department were enrolled in the study. Informed consent was taken. Clearance was taken from the local ethical committee. A complete history including the patient's age, sex, marital status, residence and occupation; duration of urticaria; history of atopy (like asthma, rhinitis, hay fever); thyroid symptoms (heat/cold intolerance, sweating, sleep appetite, bowels); acid peptic disease or post-prandial distension, constipation; photosensitivity, arthralgia or arthritis, Raynaud's phenomenon; urinary symptoms; vaginal discharge; any drug intake; and exacerbating factors if any especially food or inhalant was recorded. Investigations included complete blood count with differential counts, erythrocyte sedimentation rate, peripheral blood film, renal function test, liver function test, blood sugar estimation, anti-nuclear antibody, stool examination and thyroid function test. Autologous serum skin test was done in all the patients. Montelukast in a dose of 10mg/day in adults, 5mg in the age group 6-13 years, 4mg in the age group of 2-6 years was administered for a period of twelve weeks and levocetirizine 5mg/day was added if patients developed new weals while on therapy. All medications like steroids or any other anti-histamines were withheld for a period of four weeks prior to the study.

The response at every 2 week interval and at the end of twelve weeks was noted as good (no weals in a 2 weeks period), moderate (occasional weals in a 2 weeks period) and nil (no response at all).

Results (Tabl. I)

The study group comprised of 35 patients of chronic urticaria. They included 21 females and 14 males with an age range of 14-80 years (average 35 years). Duration of urticaria ranged from 2 months to 20 years. Atopy in the form of allergic rhinitis, atopic eczema or asthma was seen in 4 patients and was associated with a longer duration of urticaria (maximum 20 years). Five patients, all females, had symptoms of and a biochemical profile of hypothyroidism. Photosensitivity was seen in 1 male. Ten female patients and 2 male patients gave a history of arthritis/arthalgias. Acid peptic disease and post-prandial distension was seen in 12 patients (8 females and 4 males) and constipation (habitual) in 12 (8 females and 4 males). Raynaud's phenomenon was seen in 1 female. Recurrent urinary tract infections or nephrolithiasis was seen in 6 patients. In 2 females, leucorrhea with smear positive for Trichomoniasis and Candidiasis was seen. Sixteen patients gave a positive drug history including non-steroidal anti-inflammatory drugs [9], anti-tubercular treatment [1], anti-depressants [5], Unani medicines [1], and benzathine penicillin [1]. Exacerbating factors included dust [2] and egg [1]. Associated diseases were lichen planus, hepatitis, sinusitis, vitiligo and rheumatic heart disease. Angioedema was seen in 2 patients. Autologous serum skin test was positive in 5 patients (4 males and 1 female) and these patients had a long duration of urticaria. Stool examination revealed *Giardia*/*Ascaris* infestation in 4.

All these patients were put on Montelukast. Out of 35 patients only 31 completed the study, 4 patients were lost to follow up. Response was judged at 2 weeks, 6 weeks, and 12 weeks. 22 patients showed a good response with occasional weals at the end of 2 weeks and no weals at the end of 12 weeks. These included all 8 patients on NSAIDs.

Four of these relapsed on discontinuation of therapy-1 just a week later and 3 after 4 months. A moderate response was seen in 4 patients. Five patients had persistent urticaria (response nil). They included patients with chronic urticaria of many years duration or with underlying atopy and/or ASST positive patients.

Associated features	Number of patients
Atopy	4
Hypothyroidism	5
Photosensitivity	1
Arthralgia or arthritis	12
APD or PPD	12
Constipation	12
Raynaud's phenomenon	1
UTI or nephrolithiasis	6
Leucorrhoea	2
Drug intake	16
Angioedema	2
ASST	5

Table I. The various factors present in the study group of chronic urticaria patients

Discussion

Chronic urticaria is defined as the appearance of pruritic weals on the body, daily or on most days of a week for a period greater than six weeks. The term chronic urticaria encompasses a variety of different disorders with diverse etiologies and presentations that share wealing as the most common clinical feature. These include the physical urticaria, autoimmune urticaria and chronic idiopathic urticaria (CIU). Co-existence of physical urticaria with CIU or autoimmune urticaria occurs frequently. Angioedema occurs concurrently with chronic urticaria in 87% patients with CIU and is also frequent in autoimmune urticaria. An overall average lifelong prevalence of chronic urticaria is estimated to be about 1-2%. Urticaria can be highly distressing and can cause personal, social and occupational disability [1-4].

Most patients with chronic urticaria have been found to have an endogenous rather than an exogenous cause of illness. There is a wide range of secondary external aggravating factors that can bring out weals and angioedema in patients with chronic urticaria especially pressure; friction; drugs eg NSAIDS; foods and food additives like tartrazine and other azo dyes; infections/infestations like intercurrent viral infections, intestinal parasites; inhalants like grass pollen, animal danders, house dust; implants like metal pin, metal dental prosthesis and systemic diseases especially connective tissue diseases [5-8].

A good number of cases may be idiopathic with auto immunity being recognized as an increasingly important cause. Sera of approximately 60% of patients with chronic urticaria cause a pink weal, probably due to histamine release, when injected intradermally into the patient's own skin (the autologous serum skin test). Infact sera of about 30-50% patients with chronic urticaria released histamine in vitro from basophils and skin slices obtained from healthy people implying presence of circulating serum histamine releasing factor. This activity has been found to be due to functional IgG antibodies directed against α-subunit of high affinity IgE receptors (FcεRI-α) or less frequently against receptor bound IgE. In some patients the histamine-releasing factor is mast cell specific and is a non-immunoglobin which is not inhibited by preincubation with FcεRI or IgE [9-13].

It has also been found that normal subjects with history of acute urticaria induced by several NSAIDs show a positive reaction to intradermal injection of autologous serum, a phenomenon observed in patients with CIU and suggests a possible common background in CIU and NSAID induced urticaria. A relation between these two conditions is further suggested by the fact that up to 30% of the patients with chronic urticaria have worsening of their skin disorder after ingestion of chemically unrelated NSAIDs. A study conducted in these normal subjects with NSAID intolerance revealed a propensity to develop chronic urticaria in 33% over a follow up period of 1-10 years [14].

The treatment of chronic urticaria can be quite challenging. Anti-histamines are the first-line treatment for all patients with chronic urticaria. Three main groups of anti-histamines used singly or in combination include the classical sedating H1, non-sedating second generation H1 and their derivatives and the H2 antihistamines. Second generation anti-histamines are preferred to first generation H1 anti-histamines in the treatment of chronic urticaria because of their lack of sedation, impairment of cognitive and psychomotor performance and other side effects. In a fraction of cases treatment is inadequate. In these patients with unremitting disease, non- conventional modalities are tried. These include dapsone, doxepin, epinephrine, prednisolone, sulfasalazine, thyroxine, montelukast, cyclosporine, intravenous immunoglobulins, plasmapheresis and immunosuppressants [15,16].

As urticaria symptoms can have a profound effect on a patient's quality of life (QoL); therefore, treatment should address both relief of physical symptoms and improvements in QoL. Erbagci Z. [17] conducted a randomized single-blind placebo-controlled study in 30 patients of chronic refractory urticaria. The medication was given in a cross-over manner over 12 weeks as adjunctive treatment to an anti-histamine (H1). After informed consent, 2 groups were made. Group A received montelukast 10 mg once a day for six weeks followed by crossover to 6 weeks on placebo and a non-sedating antihistamine as needed. In Group B administration was reversed. Urticaria activity score (UAS) and visual analogue score (VAS) was used to monitor the response. No side effects were noted. H1 antihistamine intake was significantly less frequent during montelukast period ($p<0.01$). Statistically significant difference in UAS and VAS ($p<0.01$, $p<0.05$) between montelukast and placebo periods was seen. Thus montelukast was found to be a safe and effective adjuvant to anti-histamines in urticaria.

In our patients montelukast was effective in majority of cases and the adjunctive intake of levocetirizine was reduced. Moreover the drug was well-tolerated with minimal side-effects. It was found especially useful in the patients on NSAIDS. Urticaria has been known to be caused by a number of pathophysiological mechanisms. These include immunological IgE and IgE-receptor dependent urticaria; urticaria mediated by complement and other effector systems; urticaria after direct mast cell degranulation; urticaria relating to abnormalities of arachidonic acid metabolism and idiopathic urticaria. Leukotrienes play a pivotal role in NSAID induced urticaria. Leukotriene receptor antagonists block the action of these and hence their benefit in aspirin sensitive urticaria.

In our study twenty-two patients had a good response, four showed moderate and five patients had no response. A quick relapse was seen in atopics and ASST positive patients indicating perhaps the need for a longer therapy.

In conclusion montelukast seems a promising option both in terms of safety and efficacy in chronic urticaria. It is well worth a trial in these patients.

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