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### Efficacy of montelukast, in combination with loratadine, in the treatment of delayed pressure urticaria

#### To the Editor:

Delayed pressure urticaria (DPU) is a type of physical urticaria characterized by the gradual onset of wheals or edema in areas where pressure has been applied to the skin. Usually, antihistamines alone are insufficient to control DPU; accordingly, corticosteroids might be beneficial to all patients with this disease, though it is associated with undesirable side effects. Montelukast is a cysteinyl leukotriene receptor (CysLT1) antagonist. Cysteinyl leukotrienes—LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>—are strong smooth muscle constrictors and contribute to the onset of inflammation by causing plasma extravasation and eosinophil recruitment.<sup>1</sup> CysLT1 antagonists, given concomitantly with H<sub>1</sub>-receptor antagonists, have been shown to be effective in the treatment of chronic asthma and chronic urticaria.<sup>2,3</sup> The objective of our study was to evaluate the efficacy of the combination of montelukast and loratadine as therapeutic agents for DPU.

Twenty subjects (5 male and 15 female) affected by DPU were recruited. They ranged in age from 18 to 68 years (mean age, 45.5 ± 15.17 years). One month before treatment, patients were asked to discontinue systemic corticosteroids. The study was approved by the Ethical Committee, and each subject signed an informed consent form. Exclusion criteria were as follows: inability to understand the nature and scope of the study and/or evidence of an uncooperative attitude; cardiac, renal, hepatic, or rapidly progressing fatal disease; a history of alcohol consumption or hypersensitivity to montelukast or loratadine; pregnancy; pregnancy potential; current lactation.

After a careful history was taken and an accurate physical examination was performed, a challenge test was used to confirm the diagnosis of DPU. For the diagnosis of DPU, a 7-kg weight was suspended from the patient's shoulder for 15 minutes and readings of the test area were done at 0.5, 3, 6, 8, and 24 hours. Results were graded on a scale of 0 to 3, as follows: 0, severe response; 1, mod-

erate response; 2, mild response; 3, no response.<sup>4</sup> The study was conducted in a randomized, double-blind fashion; results were evaluated on an intention-to-treat basis.

After diagnosis, each patient was randomly assigned to receive either loratadine 10 mg (n = 10) or loratadine 10 mg plus montelukast 10 mg (n = 10) for 15 days. At randomization, the baseline characteristics of the 2 groups were matched. Pressure-testing was repeated at baseline and after treatment and evaluations were made at each visit by the same investigator for each patient. Blood tests were performed (total blood cell count and blood chemistry [aspartate transaminase, total bilirubin, creatinine and urea]) at baseline and at the end of the study. Statistical analysis was performed with the Fisher exact test for 2 × 2 contingency tables (0-2, positive response; 3, no response). A probability of *P* < .05 was taken as statistically significant.

All 20 patients completed the study. Twelve patients (60%) had concurrent chronic idiopathic urticaria and/or dermatographism.

In this study, after challenge testing had been carried out at the end of the treatment, montelukast + loratadine was significantly more effective (*P* < .05) than loratadine alone. In fact, rechallenge testing revealed a total suppression of response after 3 to 6 hours in 8 patients (80%) from the montelukast + loratadine group and after 6 hours in 2 patients (20%) from the loratadine group. In contrast, 1 patient in the loratadine group and 1 patient in the montelukast + loratadine group had a moderate response, whereas 7 patients in the loratadine group and 1 patient in the montelukast + loratadine group had a mild response or no response. Blood chemistry tests conducted at the end of treatment revealed no changes in any of the studied patients, and no serious adverse effects were observed by the investigator or reported by the patient, confirming the tolerability of montelukast and loratadine. Somnolence was reported only in 2 patients receiving montelukast + loratadine.

The pathogenesis of DPU remains unclear. Characterized by a late-phase-type reaction occurring several hours after the application of weight, DPU is a disorder in which lymphocytes, eosinophils, mast cells, and mediators play an important role. Other authors have hypothesized that leukotrienes (particularly LTB<sub>4</sub>) might play a role in such reactions.<sup>5</sup> Increased levels of LTE<sub>4</sub> were observed in patients with cold urticaria and atopic dermatitis,<sup>6,7</sup> and injection of the CysLTs into human skin produced a wheal and flare reaction.<sup>8</sup>

The anti-inflammatory potential of anti-leukotrienes in asthma has been confirmed in a number of studies.<sup>2,9</sup> In vitro, it has been demonstrated that loratadine induces a reduction in LTB<sub>4</sub> levels<sup>10</sup>; in vivo, loratadine has been shown to inhibit histamine release and to decrease eosinophils counts in blood and sputum.<sup>11</sup> CysLT1 antagonists, such as montelukast 10 mg, have been shown to be effective with or without antihistamines in patients with chronic urticaria.<sup>3,12</sup> The effect of leukotriene antagonists in the control of chronic urticaria has not been extensively studied.

This is the first study to demonstrate the therapeutic benefit of montelukast given concomitantly with loratadine in patients affected by DPU. Indeed, the favorable response to montelukast + loratadine might reflect the involvement of leukotrienes in the pathogenesis of DPU. It could also suggest that leukotriene antagonists might have a potential role in the treatment of inflammatory skin diseases. Despite the limitations of this preliminary report (eg, there was no placebo control difference in DPU with or without chronic urticaria), our results are encouraging. Therefore, we believe that more studies are needed to evaluate the efficacy of the concomitant administration of montelukast and loratadine in the treatment of DPU.

Eustachio Nettis, MD  
Alessandro Pannofino, MD  
Elsa Cavallo, MD  
Antonio Ferrannini, MD  
Alfredo Tursi, MD  
Cattedra di Allergologia e Immunologia Clinica  
Padiglione Chini-Policlinico  
University Of Bari  
Italy

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#### ***Penicillium nalgiovense* as an occupational and contact allergen**

To the Editor:

Molds comprise a taxonomic kingdom, with many

species ubiquitous in nature. Different studies have shown an association between respiratory allergic disease and exposure to fungi. The implication of fungi as occupational or food allergens is much more limited. Thus the exposure to *Plasmopara viticola* has been related to the respiratory symptoms of a greenhouse worker,<sup>1</sup> and the ingestion of champignon has been implicated in oral allergy syndrome.<sup>2</sup>

Processed cold meat manufacturers use mold cultures that are incorporated into the meat and on the outside of the casing to achieve the final aroma and flavor of the sausage and to protect it from wild mold growth. Commercially produced mold cultures of *Penicillium nalgiovense*, *Penicillium expansum*, or *Penicillium chrysogenum* are usually inoculated. This process could expose workers to high quantities of spore dust and cause hypersensitivity pneumonitis.<sup>3</sup>

We describe here a case (patient 1) of occupational asthma in a pork butcher caused by *P nalgiovense*, as well as a case (patient 2) of contact urticaria related to *P nalgiovense* sausage casing.

Patient 1 was a 45-year-old male pork butcher who had experienced cough, tightness of the chest, and sibilant dyspnea during the last 2 years. Episodes were related to the handling of sausages and inhalation of the dust coming from the sausage casings at his work in the butcher's area of a supermarket.

Patient 2 was an 18-year-old woman who reported pruritus, facial erythema, and bilateral palpebral angioedema after touching the casing of sausages, although she tolerated their ingestion.

Samples of white dust from the sausage casings were placed on Petri dishes containing bacto-potato dextrose agar supplemented with 1 g/L yeast extract. The plates were incubated at 20°C. A unique fungus grew in all the dishes. The colonies attained a diameter of 20 mm in 14 days, showing slight radial furrows that were at first white and then slightly yellow-orange in color. The colonies were identified as *P nalgiovense*.<sup>4</sup> Portions of the edge of the colony were transferred to slants of the same culture medium for mycelium production.

Samples of white dust from the sausage casings were examined with an electron microscope, and the morphology of the penicillia and the conidia matched the description of *P nalgiovense*.<sup>4</sup>

Exposure to fungal spores at the pork butcher's area was assessed before and during his working activity by using a volumetric sampler (Biotest RCS, Biotest AG) equipped with an agar strip specific for the determination of molds (Agar strip YM, Art. No. 941200). Air volumes of 0.1 m<sup>3</sup> were sampled at a flow rate of 50 L/min. A high concentration of fungal spores (2400 cfu/m<sup>3</sup> of air), which were identified as *P nalgiovense*, was detected in the samples taken during the butcher's working activity. Almost no spores were observed in the samples taken before starting work.

Freeze-dried mycelium from *P nalgiovense* isolated from the sausage casings was extracted at 10% wt/vol in 1.8% NaCl for 90 minutes. After centrifuging, the super-