

cal, Rockford, Ill) 1:2500 diluted in the blocking buffer. Bands were visualized through use of an ECL Western Blotting kit (Amersham, Buckinghamshire, United Kingdom). Densitometric analysis of protein bands was performed through use of the program UVISoft-UVIb (UVI Tech, Cambridge, United Kingdom).

Six sera were randomly selected from a wider population of patients with clinical histories of rhinitis and/or rhinoconjunctivitis as well as specific IgE antibody and skin prick test results that were positive to chenopod pollen extract. Titers of specific IgE antibodies of these sera to chenopod pollen extract, determined by means of the CAP technique (Pharmacia, Uppsala, Sweden), ranged from 19.4 to 53.9 kU/L, and the media of the 6 sera was 38.25 kU/L. An equivolumetric pool of these sera was used to perform immunoblotting assays.

IgE binding to the protein extract obtained from *Chenopodium album* pollen after SDS-PAGE and transferred to membranes showed strongly reactive protein bands at 10 kd and 14 to 16 kd, as well as other minor IgE binding components of higher molecular mass (Fig 1, B).

IgE immunoblotting inhibition assays were performed, alternatively, with 2 µg of purified olive profilin⁶ or 1 µg of olive polcalcin.⁷ As a positive control, 500 µg of the *C album* pollen extract was used as an inhibitor. The percentage of inhibition was calculated by densitometry of protein bands before and after inhibition assay. Olive profilin was able to inhibit 73% of the IgE-binding capability of the sera to the 14- to 16-kd band, and olive polcalcin reached up to 100% of inhibition of the corresponding band (Fig 1, B), indicating the presence of homologous proteins in the chenopod pollen. Chenopod extract rendered complete inhibition of the IgE-binding bands.

These results indicate that the panallergens profilin and polcalcin should play a main role in the allergenicity to Chenopodiaceae species and should be involved in extensive cross-reactivity processes. By contrast, Che a 1 would represent a primary inductor of allergy, inasmuch as it exhibited no significant IgE cross-reactivity with other pollen sources.⁵ The data presented in this work might help to simplify diagnosis and therapy of pollinosis.

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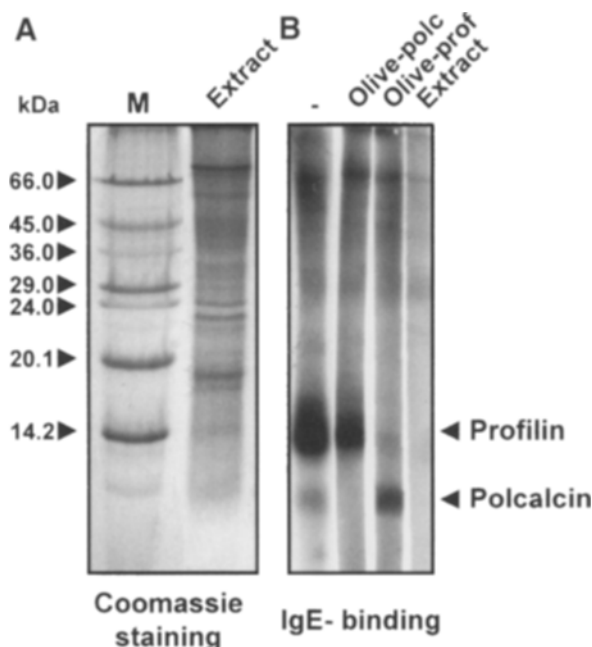


FIG 1. SDS-PAGE analysis of chenopod pollen extract. **A**, Coomassie Blue staining. **B**, IgE binding inhibition assays to chenopod pollen extract, without (-) and with inhibitors: olive profilin, olive polcalcin, and whole chenopod protein extract.

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A possible role for cyclooxygenase 2 inhibitors in the treatment of chronic urticaria

To the Editor:

Adequate control of chronic urticaria can be frustrating for both the patient and the physician. Currently, standard treatment is aimed at blocking the effects of histamine released from cutaneous mast cell degranulation.^{1,2} Many patients will not get adequate relief from type 1 and type 2 antihistamines alone and might benefit from the addition of a leukotriene pathway modifier.³ Patients whose symptoms are not adequately controlled with these medications often require oral glucocorticosteroids.^{1,2} More aggressive therapies, such as cyclosporine, intravenous gammaglobulin, or plasmapheresis, might be necessary.²

TABLE I. Summary of the patients on the basis of patient demographics, relevant medical and social history, medication regimen before starting rofecoxib, dose and effect of rofecoxib on symptoms and dosage of other medications, and adverse effects from the medications used to treat the urticaria

Patient	Age (y)/sex	Duration of urticaria/ relevant history	Regimen before rofecoxib	Dose of and result with rofecoxib	Adverse treatment effects
1	50/F	6 mo/Hashimoto thyroiditis	Levothyroxine, cetirizine, ranitidine, montelukast, prednisone	25 mg PO qd; hives resolved; off prednisone	20-lb weight gain w/prednisone
2	58/F	7 y/hepatitis B carrier	Cetirizine, ranitidine, montelukast, prednisone	25 mg PO qd; hives resolved; off prednisone	Edema, ↑Cr w/rofecoxib from 1.3 mg/dL to 2.1 mg/dL
3	57/M	3 y/airline pilot	PRN H ₁ blockers, fexofenadine, cetirizine, prednisone, montelukast, cimetidine	25 mg PO qd; hives resolved	Irritability, weight gain w/prednisone; somnolence w/H ₁ blockers
4	18/F	3 mo/student	Cetirizine, ranitidine, montelukast, doxepin, prednisone	25 mg PO qd; hives resolved; off prednisone	Sedation w/H ₁ blockers
5	47/M	2 y/+ANA and antithyroid antibodies, urticarial vasculitis	Prednisone, doxepin, hydroxychloroquine, montelukast, levothyroxine, PRN diphenhydramine	25 mg PO qd; hives improved, (see Table II)	60-lb weight gain, HTN, GERD w/ prednisone
6	42/F	2 ½ y	Cetirizine, ranitidine, fexofenadine, montelukast	25 mg PO qd; no change	
7	23/M	6 wk/antithyroid antibodies	Doxepin (levothyroxine started after rofecoxib)	50 mg PO qd; no change	Somnolence from H ₁ blockers
8	45/M	4 y/Crohn's disease, Hashimoto's thyroiditis	Levothyroxine, doxepin, prednisone, montelukast	25 mg PO qd; no change	Iatrogenic hyperthyroidism

PO, By mouth; qd, every day; Cr, creatinine; PRN, as needed; ANA, antinuclear antibody; HTN, hypertension; GERD, gastroesophageal reflux disease.

Mast cell degranulation resulting in histamine release is a key factor in chronic urticaria.^{1,2} It is unknown, however, whether production of prostaglandins and cysteinyl leukotrienes by mast cells is also important. Cutaneous mast cells can produce prostaglandin D₂ (PGD₂), which is primarily synthesized by cyclooxygenase 2 (COX-2), and leukotriene C₄ (LTC₄), which is synthesized through the lipoxygenase pathway.⁴⁻⁶ Both elicit wheal-and-flare reactions when administered intradermally to healthy volunteers.⁷ Cyclooxygenase 1 (COX-1), on the other hand, produces PGE₂, which is believed to downregulate the synthesis of LTC₄.⁸ Classic nonsteroidal anti-inflammatory drugs block both cyclooxygenase enzymes, thereby inhibiting synthesis of both PGD₂ and PGE₂. Nonsteroidal anti-inflammatory drugs can be a cause of urticaria themselves.

Using the rationale that a COX-2 inhibitor would inhibit the production of PGD₂ while maintaining the production of PGE₂ (and theoretically limiting production of LTC₄), it seemed plausible that COX-2 inhibitors would be a useful addition to the mediator blockade therapy of chronic urticaria. For this reason, we have added rofecox-

ib (open label) to the regimen of 8 patients with refractory chronic idiopathic urticaria. Table I summarizes these cases on the basis of patient demographics, relevant medical and social history, medication regimen before starting rofecoxib, dose and effect of rofecoxib on symptoms and dosage of other medications, and adverse effects from the medications used to treat the urticaria. The evaluation of these patients included the following laboratory studies: complete blood cell count, liver function testing, thyroid stimulating hormone measurement, anti-thyroid antibody measurement, anti-nuclear antibody measurement, complement level measurement, sedimentation rate measurement, and urinalysis. All significant findings are noted in Table I. Table II summarizes the clinical course of the patients who responded to rofecoxib.

Of the 8 patients, 5 (patients 1-5) had complete resolution of their hives and were able to discontinue steroids. The symptoms of patient 5, who had urticarial vasculitis, improved after rofecoxib treatment, and the patient was able to decrease his steroid dose initially. However, he had to increase it again after he temporarily discontinued the rofecoxib. After restarting the rofecox-

TABLE II. Clinical course of the responders

Patient	Follow-up after initiation of rofecoxib	Clinical course	Recurrence of hives	Remaining medications
1	1 y	Tapered off prednisone within 3 mo after adding rofecoxib, then off other medications	No	Levothyroxine
2	7 mo	Rofecoxib discontinued within 1 mo because of adverse effects	Yes	Cetirizine, ranitidine, montelukast; restarted prednisone
3	8 mo	Discontinued prednisone before initiation of rofecoxib because of side effects; tapered off most medications within 6 months of adding rofecoxib	Yes, with attempts to taper off fexofenadine or rofecoxib	Fexofenadine and rofecoxib
4	2 y	Discontinued all medications within 2 mo of adding rofecoxib	No	
5	17 mo	A. Reduced prednisone dose within 3 mo of adding rofecoxib. B. Tapered off prednisone within 3 months of restarting rofecoxib and with dose adjustment of levothyroxine and hydroxychloroquine.	A. Yes, when rofecoxib was temporarily discontinued. B. No further recurrences.	Levothyroxine, doxepin, fexofenadine, ranitidine, celecoxib*

*This patient eventually stopped rofecoxib after discontinuation of prednisone and had no recurrence of his urticaria. Shortly thereafter, however, he developed arthralgias and myalgias and was prescribed celecoxib.

ib, he was eventually able to discontinue prednisone altogether (Table II). All 5 of the patients whose symptoms improved after rofecoxib treatment had improvement within the first 5 to 7 days. The remaining patients (patients 6-8) had no improvement (Table I).

These patients exemplify some of the frustrations associated with the treatment of chronic urticaria. Most had adverse effects related to their therapy, many from corticosteroids. Patients 3 and 4 have occupations in which they cannot tolerate the sedative effects of type 1 antihistamines. Patient 8 was so frustrated with his chronic urticaria that he took high doses of levothyroxine in an attempt to control it, causing symptoms of diarrhea, anxiety, and tremor.

Patient 2 demonstrates that rofecoxib is not without its own risks. It can adversely affect renal function and cause hypertension and edema. In addition, there have been rare reports of anaphylaxis⁹ and urticaria^{10,11} caused by this drug. It is also interesting to note that COX-2 overexpression has been found in premalignant and neoplastic lesions. Preliminary evidence suggests that COX-2 inhibitors might have a protective role in preventing colon, breast, lung, esophageal, and oral tumors.¹² It is plausible that a patient with an underlying malignancy associated with increased COX-2 expression might experience urticaria as a result of excess PGD₂ production. In this scenario, the use of rofecoxib could both suppress an occult malignancy and control the urticaria.

A case like this should be uncommon, however, because there is no statistical relationship between chronic urticaria and diagnosis of malignancy.¹³ Nonetheless, one should always obtain an appropriate cancer history (including family history) from these patients and ensure that they are up to date on the age- and sex-appropriate cancer screening as part of the work-up for chronic urticaria.

The hypothesis that urticaria can be controlled by the addition of a selective COX-2 inhibitor to concurrent antimediation blockade is supported by the available data on the mechanism of action of corticosteroids. Studies examining the effects of steroids have found that they block the induction of *COX2* gene expression with little or no effect on *COX1* gene expression,⁶ and there is no effect of oral steroids on skin mast cell numbers.¹⁴ Thus, the efficacy of controlling urticaria with steroids might be, at least in part, related to the inhibition of COX-2 without affecting COX-1.

One might argue that the patients whose hives resolved after starting rofecoxib might have reached the point in their clinical course at which their urticaria spontaneously resolved. This could have been the case with our patients; however, patient 5 did experience worsening symptoms after stopping the rofecoxib, and his symptoms improved again when it was restarted. Patient 3 also had recurrence of his urticaria when he attempted to taper off the rofecoxib.

The addition of rofecoxib to an antimediation treatment regimen seemed to help some, but not all, of our patients with severe chronic urticaria and allowed them to taper their corticosteroid use. Although not without risks, rofecoxib might be useful in helping patients reduce some of the other medications that have undesirable effects. We have not tried other selective COX-2 inhibitors, such as celecoxib, meloxicam, or valdecoxib. Some of these have higher COX-1 inhibition than rofecoxib¹⁵ and thus might not be as effective. Double-blind, placebo-controlled trials are needed to determine whether COX-2 inhibitors truly have a role in treating chronic urticaria.

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