

Effects of fexofenadine and other antihistamines on components of the allergic response: Adhesion molecules

Giorgio Ciprandi, MD, Maria Angela Tosca, MD, Cristina Cosentino, MD,
Anna Maria Riccio, PhD, Giovanni Passalacqua, MD, and
Giorgio Walter Canonica, MD *Genoa, Italy*

Intercellular adhesion molecules (ICAMs), in particular ICAM-1, appear to play a crucial role in the recruitment and migration of inflammatory cells to the site of an allergic reaction. Glucocorticoids and allergen-specific immunotherapy have been shown to exert effects on selected components of this system, both *in vitro* and *in vivo*, but further research is required to better understand the effects of these therapies. Nasal and conjunctival challenge models (including natural and experimental allergen exposure) represent useful and safe tools for studying the activity of antiallergy drugs *in vivo*. These tests allow the investigation of a wide variety of parameters including inflammatory infiltrate, ICAM-1 expression, and changes in the concentration of soluble inflammatory mediators. With these tools, anti-inflammatory activity related to the modulation of epithelial cell adhesion molecules has been demonstrated *in vivo* for several H₁-receptor antagonists (azelastine, cetirizine, loratadine, levocabastine, oxatomide, and terfenadine). Fexofenadine is a nonsedating, long-acting antihistamine with highly selective H₁-receptor antagonist activity and a particularly favorable safety profile. In addition, fexofenadine has proven anti-inflammatory activity and has been shown to inhibit a number of mediators at clinically relevant concentrations, including *in vitro* inhibition of ICAM-1 expression on conjunctival and nasal epithelial cells. (*J Allergy Clin Immunol* 2003;112:S78-82.)

Key words: Antihistamines, allergic inflammation, intercellular adhesion molecules, ICAM-1

The mechanisms regulating allergic inflammation have been extensively investigated during the last 10 years. Although mast cells, which release histamine and other mediators after allergen-IgE binding, remain the primary trigger of the allergic response, a wide variety of cells and mediators (eg, T lymphocytes, eosinophils, leukotrienes, cytokines, chemokines, and adhesion molecules) are also involved in the allergic response.

Mast cell activation is responsible for the clinical aspects of the early-phase reaction (EPR), whereas the selective recruitment and activation of inflammatory cells sustain the late-phase reaction (LPR), leading to tissue damage. Leukocyte migration and selective recruitment at

Abbreviations used

CAM:	Cell adhesion molecule
ELAM-1:	Endothelial-leukocyte adhesion molecule
EPR:	Early-phase reaction
ICAM-1:	Intercellular adhesion molecule 1
LFA:	Leukocyte functional antigen
LPR:	Late-phase reaction
MPI:	Minimal persistent inflammation
SAR:	Seasonal allergic rhinitis
VCAM:	Vascular cell adhesion molecule

the site of allergic inflammation are governed and controlled by the adhesion molecule system. This system was characterized during the early 1980s when a group of molecules that appeared to mediate intercellular adhesion were discovered; these have subsequently been given the collective term *cell adhesion molecules* (CAMs).¹

The epithelial expression of a number of CAMs, and intercellular adhesion molecule 1 (ICAM-1) in particular, was subsequently identified as a reliable marker of ongoing allergic inflammation² and therefore presented a promising therapeutic target.

CAMS: CLASSIFICATION AND FUNCTION

CAMs are a heterogeneous group of molecules, but their structural and chemical diversity is balanced by their common functionality. They are responsible for intercellular adhesion; cell adhesion to epithelia, endothelia, and extracellular matrix; cellular recruitment; selective migration; homing; tissue architecture maintenance; and healing. The flexibility of this system is due to several characteristics: (1) the differential distribution of CAMs on different cell types, (2) the possible modulation of CAM expression by inflammatory mediators (inducibility), and (3) the existence of soluble forms of CAMs that might act as an internal regulatory element.

CAMs are subdivided into large families of molecules on the basis of their structural characteristics (Table I). ICAM-1 seems to have a pivotal role in allergic inflammation, because it is promptly expressed on epithelial cells after allergen exposure. Selectins are also promptly expressed on leukocytes and endothelial cells and mediate the early phases of adhesion after exposure to inflammatory stimuli.

The selective expression pattern and modulation of CAMs partly explain the migration and recruitment of

From Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genoa.

Reprint requests: Prof G. W. Canonica, MD, Allergy and Respiratory Diseases, DIMI, Pad Maragliano, L go R Benzi 10, 16132 Genoa, Italy.

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TABLE I. Classification of cell adhesion molecules

	Immunoglobulin superfamily	Integrins	Selectins
Structural characteristics	Glycoproteins with an immunoglobulin-like structure	Non-covalent heterodimers of an α and β chain	N-terminal lectin domain
Key family members	Immunoglobulins, TCR, CD3, MHC, CD4, CD8, LFA-2, LFA-3, ICAM-1	β 1-integrins or VLA, β 2-integrins or leukocyte integrins (expressed on leukocytes), β 3-integrins or cytoadhesins (expressed on endothelial cells and platelets)	P-, E-, L-selectin, cadherins

TCR, T-cell receptor; VLA, very late antigen.

inflammatory cells at sites of allergic reaction. This mechanism has been well elucidated for eosinophils (and other leukocytes) in asthma.^{3,4}

EPITHELIUM AND CAMS

The epithelium expresses varying numbers of several different adhesion molecules, and this expression can be modulated by inflammatory mediators. Conjunctival and nasal provocation tests represent an ideal model for studying allergic inflammation because of their simple execution, reproducibility, and safety.^{5,6} In addition, these procedures are well tolerated by patients and allow the use of a wide variety of specific and nonspecific stimuli, including allergens, hyperosmolar solution, and histamine. Furthermore, conjunctival and nasal scrapings can be obtained from subjects at baseline, after challenge, and under natural allergen exposure.

When allergen is administered to the nose or conjunctiva, the EPR occurs within minutes and is manifested by the clinical symptoms of sneezing, rhinorrhea, and nasal obstruction or conjunctival hyperemia and lacrimation. The clinical reaction is accompanied by a cellular infiltrate of the epithelia and the prompt expression of ICAM-1. The EPR quickly subsides and, during the following 6 to 12 hours, the LPR occurs in which eosinophils are the predominant cell type. In contrast to the EPR, the LPR subsides slowly; in the nose the clinical LPR is not always detectable, but tissue inflammation is always present.

Allergic subjects show nasal/conjunctival inflammation (the presence of inflammatory cells and ICAM-1 expression) during natural allergen exposure.^{5,6} Interestingly, in subjects with an allergy to house dust mites who are persistently exposed to this allergen, minimal persistent inflammation (MPI) is detected even when they are symptom free.⁷ More recently, MPI has also been detected in subjects with pollen allergy.⁸

Thus, ICAM-1 might be used as a reliable marker of clinical and subclinical inflammation. Of note, ICAM-1 is a selective receptor for human rhinoviruses. Because rhinoviral infections are the most frequent event preceding asthma attacks in children, the continuous expression of ICAM-1 on epithelial cells in symptom-free allergic subjects should be regarded as a possible triggering event for asthma attacks.

CORTICOSTEROID MODULATION OF CAMS

It is well established that the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and the expression of endothelial-leukocyte adhesion molecule (ELAM-1) and ICAM-1 at the genomic level.⁹ Glucocorticoids might also have an inhibitory effect on neutrophil, eosinophil, and monocyte CAMs, as a result of the transcriptional suppression of CAM genes via nuclear factor kappa beta and the inhibition of IL-2, IL-7, and IL-15 synthesis. In addition, glucocorticoids might also induce anti-inflammatory molecules such as annexin I, which is thought to be involved in all steps of the adhesion cascade.¹⁰

Glucocorticoids have been evaluated for their effects on CAMs in asthma and allergic rhinitis both in vitro and in vivo. Pretreatment with hydrocortisone, dexamethasone, or mometasone furoate in vitro has been shown to decrease rhinovirus-induced ICAM-1 expression in respiratory epithelial cells, with inhibitory concentration of 50% (IC₅₀) values of between 10⁻¹¹ to 10⁻¹⁰ mol/L.¹¹ However, in bronchial epithelial cells, preincubation with 10⁻¹¹ to 10⁻⁷ mol/L fluticasone propionate did not inhibit the increase in serum ICAM-1 levels induced by TNF- α , despite the fact that the same concentration of steroid had previously been shown to effectively inhibit vascular cell adhesion molecule 1 (VCAM-1) expression in the same cell line.¹²

In children with moderate atopic asthma, inhaled budesonide (400 to 800 μ g/day for 2 months) significantly reduced serum levels of ICAM-1, and this correlated with improvements in pulmonary function.¹³ In another study of patients with asthma, oral prednisolone therapy (2.5 to 40 mg/day for 1 to 14 days) significantly decreased serum levels of soluble ICAM-1.¹⁴

EFFECTS OF IMMUNOTHERAPY ON CAMS

Immunotherapy for specific allergens has been assessed for its effects on serum levels of CAMs. In a study of patients with seasonal allergic rhinitis (SAR) receiving grass pollen-specific immunotherapy, there was a significant decrease in levels of soluble ICAM-1, which correlated with clinical outcomes (ie, symptom scores).¹⁵ Immunotherapy was again shown to decrease serum levels of ICAM-1 but not VCAM-1 in a study of children with house-dust-mite perennial allergic rhinitis.¹⁶ Another

study compared the effects of specific immunotherapy versus loratadine on serum levels of ICAM-1 and VCAM-1 in patients with mild to moderate house-dust-mite allergic rhinitis. Both treatments produced significant decreases in VCAM-1 but not in ICAM-1, with no differences between the 2 treatment groups.¹⁷

These data suggest that the effects of specific immunotherapy on serum levels of CAMs are variable and that further research is required.

ANTIHISTAMINE MODULATION OF CAMS

Several actions of antihistamines concerning mediator release and cell activation have been documented.¹⁸ The modulation of CAM expression has been demonstrated in vitro for levocabastine, fexofenadine (see later), and terfenadine¹⁹⁻²¹ on cultured human epithelial cells.

We have investigated the effects of several antihistamines on adhesion molecules in vivo by using ocular and nasal challenge models. In patients with pollen sensitivity studied outside the pollen season, the administration of azelastine to the nose and eyes reduced ICAM-1 expression after allergen-specific challenge.^{22,23} Furthermore, nasal topical azelastine reduced ICAM-1 expression and inflammatory infiltration under natural allergen exposure in pollen-induced rhinitis. This effect was more prominent when treatment was continuous rather than "as needed."²⁴ In addition, levocabastine eye drops inhibited the expression of ICAM-1 on conjunctival epithelium.²⁰ In patients with symptom-free pollen sensitivity, a 2.5-day course of cetirizine 10 mg twice a day reduced ICAM-1 expression and inflammatory cell numbers in the conjunctiva after allergen challenge.²⁵ Moreover, cetirizine has been shown to reduce ICAM-1 expression on nasal epithelial cells in patients with rhinitis during natural allergen exposure,²⁶ and, interestingly, cetirizine reduced the minimal, persistent nasal inflammation in subjects with perennial allergic rhinitis.²⁷ Oxatomide exhibited a protective effect on the conjunctiva against allergen-specific challenge, reducing inflammatory infiltrate and ICAM-1 expression in both the EPR and LPR.²⁸ During a 7-day study conducted during the pollen season in patients with pollen sensitivity, terfenadine 120 mg/day reduced inflammatory infiltration, ICAM-1 expression, and soluble eosinophil cationic protein levels in nasal lavage fluid.²⁹ Loratadine 10 mg, administered daily for 2 weeks, reduced inflammatory infiltrate and ICAM-1 expression under natural allergen exposure.³⁰ It is also suggested that loratadine can reduce the concentration of soluble mediators in nasal lavage fluid. Similar results were obtained with a conjunctival model in patients with pollen rhinoconjunctivitis.³¹

Finally, when considering the inflammatory aspects of the allergic reaction and the antiallergic activities of the newer antihistamines, the correct therapeutic approach should be to target not only the clinical symptoms but also to modulate the underlying allergic inflammation. Furthermore, the existence of MPI independent of symptomatology suggests that the long-term continuous use of these molecules is better than an "as-needed" model.

The rationale for such a strategy has been demonstrated in vivo by using long-term treatment. In a 3-month study with nasal azelastine (0.28 and 0.56 mg/day), continuous treatment during the pollen season was shown to be more effective than "as-needed" treatment in controlling both symptoms and inflammatory markers (ICAM-1 expression and cellular infiltration).²⁴ Similar results were also obtained for continuous long-term (4 weeks) treatment with cetirizine 10 mg once daily.³²

In a further study,³³ we observed that terfenadine 1 mg/kg once daily continuously administered during a 12-month period, reduced symptoms, allergic inflammation, and upper respiratory tract infection morbidity in children with allergies. These in vivo results correlate well with the expected antiallergic activity of the antihistamines reviewed and further support the need for both early and long-term treatment of allergic rhinoconjunctivitis.

FEXOFENADINE MODULATION OF CAMS

Fexofenadine is a nonsedating, long-acting antihistamine with highly selective peripheral histamine H₁-receptor antagonist activity. It is effective in the relief of SAR and chronic idiopathic urticaria symptoms.³⁴ Fexofenadine HCl has a favorable safety profile and is devoid of central nervous system effects and cardiotoxicity even at very high doses,³⁵ or when taken concomitantly with ketoconazole and erythromycin.³⁶

The antiallergic effects of fexofenadine have been studied in an in vitro model by using a continuously cultured conjunctival epithelial cell line.²¹ The human differentiated conjunctival epithelial cell line (Wong-Kilbourne) was obtained from the American Type Culture Collection (Rockville, Md). Cells were cultured in 6-well tissue culture dishes for 24 hours in the presence or absence of cytokines (IFN- γ 500 U/mL or TNF- α 200 ng/mL). Fexofenadine HCl was added to the cultures at concentrations of 0.5, 5, and 50 μ g/mL; peak plasma concentration was 441 ng/mL after a single administration of 120 mg.³⁴ ICAM-1 expression was measured by immunofluorescence flow cytometry.²¹

The results showed that fexofenadine inhibited ICAM-1 basal expression after IFN- γ stimulus at a concentration of 50 μ g/mL ($P < .03$) (Fig 1). Moreover, other immunologic parameters were studied; fexofenadine was able to decrease soluble ICAM-1 levels in IFN- γ -stimulated epithelial cells (Fig 2) and to reduce ICAM-1 expression in a fibroblast cell line (HEL) (Fig 3). Finally, fexofenadine reduced IL-6 release from fibroblasts in a dose-dependent manner. The inhibitory effect of fexofenadine on ICAM-1 expression might suggest antiallergic activity other than that mediated via the histamine H₁-receptor.²¹

SUMMARY

Adhesion molecules play a crucial role in the dynamic process of allergic inflammation, because they regulate and govern inflammatory cell migration and recruitment. In particular, ICAM-1, which is promptly expressed on

allergen exposure, is recognized as a hallmark of allergic inflammation.

Glucocorticoids and allergen-specific immunotherapy have been evaluated for their effects on serum levels of CAMs. In vitro, the effect of glucocorticoids on serum levels of ICAM-1 appears to be dependent on the stimulus for ICAM-1 expression. In vivo, it has been shown in several studies that glucocorticoids decrease serum levels of ICAM-1; the results with immunotherapy are more variable, and more research is required.

By means of in vivo nasal and conjunctival challenge models, it has been demonstrated that several of the newer antihistamines, including fexofenadine, reduce both ICAM-1 expression on nasal and conjunctival epithelial cells and inflammatory infiltration. This effect has been observed both after allergen challenge and during natural exposure and is more significant when treatment is continuous rather than intermittent.

In addition, studies have also indicated the anti-inflammatory properties of fexofenadine. In an ex vivo model, fexofenadine inhibited the histamine-induced release of β -glucuronidase and IL-6 from human macrophages and reduced hyperresponsiveness as well as inflammatory markers in an in vivo mouse model. These studies have been described fully in 2 accompanying articles in this supplement (Marone et al and Gelfand et al, respectively).

The evidence in this review therefore suggests that the treatment approaches for asthma and allergic rhinitis should include agents that have a proven effect on the modulation of CAMs.

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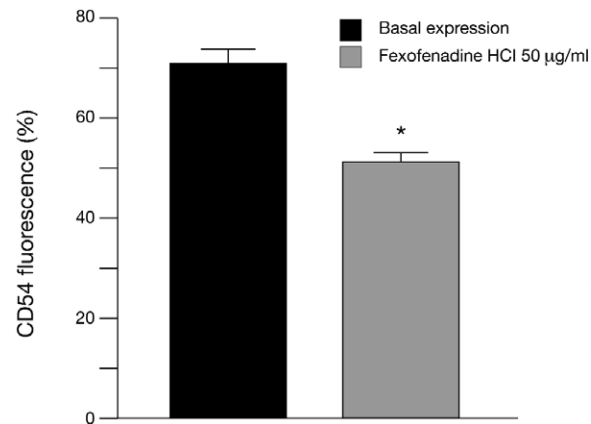


FIG 1. Effect of fexofenadine on ICAM-1 basal expression by WK cells. Data are expressed as mean $\pm$ SEM of the quantitative fluorescence values. $P < .03$. Adapted with permission from Paolieri F et al. *Ann Allergy Asthma Immunol* 1998;81:601-7.²¹

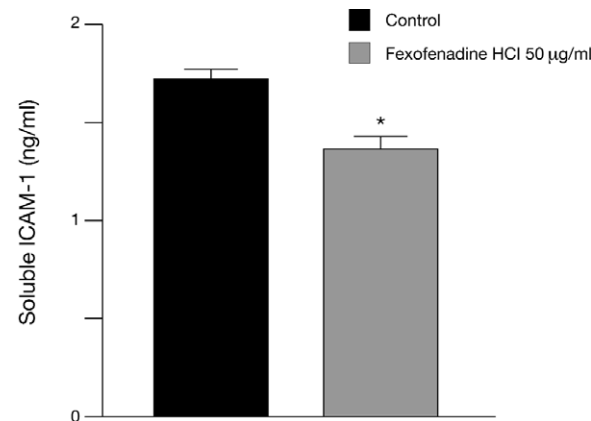


FIG 2. Effect of fexofenadine on the concentration of soluble ICAM-1 in the supernatant of IFN- γ -stimulated WK epithelial cells. Values are expressed in ng/mL. $*P < .03$. Adapted with permission from Paolieri F et al. *Ann Allergy Asthma Immunol* 1998;81:601-7.²¹

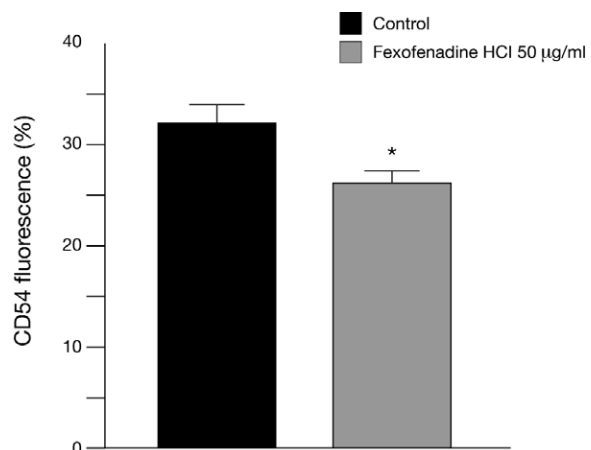


FIG 3. Effect of fexofenadine on ICAM-1 expression by IFN- γ -stimulated HEL cells. Data are expressed as mean $\pm$ SEM of the quantitative fluorescence values. $*P < .03$. Adapted with permission from Paolieri F et al. *Ann Allergy Asthma Immunol* 1998;81:601-7.²¹

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