

Prospects for antihistamines in the treatment of asthma

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Antihistamines have been evaluated as potential therapies for asthma for more than 50 years. With first-generation compounds, side effects prevented effective dosing. By reviewing published studies of the effectiveness of terfenadine, cetirizine, and loratadine in clinical asthma, evidence for the relevant effect of the second-generation antihistamines on bronchial asthma can be found. Terfenadine, at doses of 120 or 180 mg twice a day, reduced symptoms and improved pulmonary function in mild and moderate allergic asthma but was ineffective in severe perennial asthma. Fexofenadine at doses used for allergic rhinitis had little effect on seasonal allergic asthma. Research is ongoing to determine the effects of higher doses of fexofenadine. In 5 studies, cetirizine at doses of 10 to 20 mg, once or twice daily, consistently improved asthma symptoms compared with placebo or terfenadine 60 mg twice a day in 2 cases, whereas in 2 studies, loratadine at doses of 10 to 20 mg daily has not produced significant improvement in asthma. However, loratadine 5 mg combined with 60 mg of pseudoephedrine twice a day significantly improved both asthma symptoms and peak expiratory flow. Similarly, the combination of loratadine 20 mg and the leukotriene-receptor antagonist montelukast improved asthma symptoms, peak expiratory flow, and β -agonist use over montelukast alone. Therefore, there might be a role for second- and third-generation antihistamines in treating mild and moderate asthma, which might require administering doses greater than those commonly used to treat allergic rhinitis. If higher doses are sedative, the addition of decongestants or leukotriene-receptor antagonists might enhance the effects of lower doses of the antihistamines. (*J Allergy Clin Immunol* 2003;112:S96-100.)

Key words: Asthma, antihistamine, non-sedating, second-generation, leukotriene receptor antagonist, third-generation

Antihistamines have been evaluated for their efficacy in the treatment of asthma for more than 50 years.¹ Antihistamines such as chlorpheniramine were shown to produce bronchodilation when taken by mouth or intravenously,² but drowsiness limited the dose that could be administered, and in tolerated doses there was no effect on naturally occurring or exercise-induced asthma.³ Both chlorpheniramine and clemastine produced acute bronchodilation by inhalation,^{4,5} with the latter being as effective as inhaled albuterol.⁵ However, when administered by inhalation, the antihistamines tended to cause coughing.⁴ Interest in the use of antihistamines for the

Abbreviations used

Bid: Twice daily

EIB: Exercise-induced bronchoconstriction

PEF: Peak expiratory flow

treatment of asthma waned until the appearance of a second generation of drugs without the dose-limiting sedation of the earlier preparations.

Wood-Baker and Holgate⁶ compared manufacturers' recommended doses of first-generation antihistamines chlorpheniramine, brompheniramine, cyproheptadine, and clemastine and the second-generation antihistamines terfenadine, cetirizine, and astemizole with placebo for their ability to produce bronchodilation after a single oral dose. Despite a mean baseline FEV₁ of 98% of predicted, the various antihistamines produced an additional 2.6% to 9.3% increase in FEV₁. This increase was greatest for the 3 second-generation antihistamines, whereas only chlorpheniramine and cyproheptadine of the first-generation antihistamines produced significant responses. Chlorpheniramine, brompheniramine, and cyproheptadine all produced drowsiness exceeding that observed with placebo, confirming the dose-limiting side effects with these older drugs.

The acute bronchodilator responses to the individual second-generation antihistamines have been examined, often at doses exceeding those recommended for the treatment of allergic rhinitis. In 20 children, a 15% increase in predicted FEV₁ was reported at 3 hours after administration of 60 mg terfenadine.⁷ Increases in FEV₁ of 11% to 15% were observed after administration of terfenadine at doses of 60 to 180 mg in adults, compared with a decrease of 2.9% with placebo.⁸ However, there was no evidence of a dose-response relationship. Similar degrees of acute bronchodilation have been reported with 5, 10, and 20 mg cetirizine.^{9,10} Cetirizine 5 mg provided greater improvement in FEV₁ than placebo, whereas both 10 and 20 mg were more effective than 25 mg hydroxyzine.⁹ Compared with a maximum increase of 6% with placebo, the peak increase in FEV₁ with 5, 10, and 20 mg cetirizine was 13%, 12%, and 19%, respectively, showing some dose-response correlation. Compared with placebo, significant improvement in FEV₁ after administration of cetirizine persisted to the end of observations at 8 hours.¹⁰

The effect of the second-generation antihistamines on specific challenges has also been examined. In doses of 10 and 20 mg, loratadine was reported to have no effect on the early or late airway response to inhaled allergen.¹¹ Similarly, oral terfenadine in a dose of 120 mg was reported to

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TABLE I. Clinical studies in asthma with terfenadine and fexofenadine

Author	Characteristics of asthma	Drug	Dose	Duration of study	Symptoms	Lung function	β-Agonist use
Taytard et al ³¹	Mild, perennial	Terfenadine	120 mg bid	2 wk	Decreased	Improved PEF	Decreased
Rafferty et al ³²	Mild, seasonal	Terfenadine	180 mg tid	4 wk	Decreased	Improved PEF	Decreased (not significant)
Wood-Baker et al ³³	Severe, perennial	Terfenadine	120 mg bid	4 wk	Decreased nighttime awakening	No change	No change
Kaliner et al ³⁴	Moderate, seasonal	Fexofenadine	180 mg once daily	6 wk	Decreased wheezing, especially during week 1	Increased morning and evening PEF	No change

have no effect on the late response to allergen challenge.¹² However, doses of 60, 120, and 180 mg of terfenadine administered twice were reported to have a small effect on the immediate response,¹³ whereas single doses of 180 mg terfenadine were reported to significantly reduce both the early¹⁴⁻¹⁶ and the late¹⁵ response to allergen challenge. Preadministration of cetirizine, usually 15 mg twice daily (bid) for periods of 3 days to 3 weeks, repeatedly failed to diminish the early response to allergen challenge.¹⁶⁻²² In 1 study, the late response was decreased by cetirizine,²⁰ whereas in 3 other studies the late response was unaffected.^{17,18,21} In 2 studies with cetirizine in which the late decrease in FEV₁ was not reduced, there was either reduction in the postchallenge increase in methacholine sensitivity¹⁷ or in the influx of eosinophils into the bronchoalveolar lavage fluid.²¹

The potential protective effect of antihistamines has also been examined in exercise-induced bronchoconstriction (EIB). The older-generation antihistamine clemastine has been demonstrated to reduce EIB when administered by inhalation.²³ Cetirizine in single doses of up to 20 and 10 mg bid for 1 week failed to reduce EIB.^{22,24} However, when cetirizine was administered by inhalation, it reduced the exercise-induced decrease in FEV₁ by more than 50%.²⁴ Astemizole, 10 mg per day for 1 week, reduced the maximum decrease in FEV₁ from 37% to 23% in one study,²⁵ whereas in another study, 3 weeks of astemizole treatment delayed, but did not reduce, the maximum decrease in FEV₁.²⁶ Single 180-mg doses of terfenadine have significantly reduced the decrease in FEV₁ after exercise challenge in both adults^{27,28} and children.⁷

Although the bronchodilator response to second-generation antihistamines is impressive, it is not clear whether and to what extent the degree of bronchodilation observed in single-dose studies persists with repeated dosing. Spector et al¹⁰ measured the bronchodilator response to 60 and 120 mg of terfenadine, after which they administered the 2 doses bid for 1 week. After 1 week, the bronchodilator response, both in change from baseline and absolute FEV₁ achieved, was reduced from the original response and was no longer significant. Two groups of authors have commented on the failure to observe bronchodilation after the third dose of loratadine¹¹ and cetirizine,²² and

some loss of bronchodilator action with chronic administration has been suggested.²⁹

Many of the newer antihistamines have been reported to have actions in addition to histamine receptor antagonism.³⁰ These include reduced release of histamine, prostaglandin D₂, kinins, and leukotrienes and reduced expression of adhesion molecules.³⁰ In addition, cetirizine reduced eosinophil recruitment into the airways after bronchial allergen challenge.²¹

CLINICAL STUDIES OF THE EFFECTIVENESS OF ANTIHISTAMINES IN ASTHMA

Studies have been performed to evaluate the clinical effectiveness of terfenadine, cetirizine, and loratadine in asthma.

Three double-blinded, placebo-controlled studies have been performed with terfenadine (Table I). Taytard et al³¹ enrolled 52 patients with stable, mild, perennial allergic asthma. Baseline peak expiratory flow (PEF) was 82% of predicted, an average 3 puffs of salbutamol per day were used, and the mean symptom score was 2.35. After a 1-week run-in period, patients were randomly allocated to terfenadine 120 mg bid or placebo. After 2 weeks, they were crossed over to the other treatment arm for an additional 2 weeks. Terfenadine was significantly more effective than placebo at reducing mean symptom scores (1.8 vs 2.4, respectively; *P* < .01), with significant advantages for terfenadine treatment in nighttime wheezing, daytime wheezing, cough, and impairment of activities. Furthermore, there was a significantly greater reduction in mean salbutamol use (2.1 vs 2.9 puffs) and an increase in morning PEF (427 L/min vs 410 L/min) and evening PEF (437 L/min vs 430 L/min). Thus, terfenadine at doses of 120 mg bid reduced the intensity of symptoms and consumption of β-agonist while improving PEF. Rafferty et al³² studied 18 subjects with mild grass pollen-sensitive asthma in a 9-week, double-blinded, crossover study. Terfenadine was administered 180 mg 3 times daily. Compared with placebo, terfenadine significantly reduced cough by 77% and wheeze by 47%. The morning PEF rose by 5.5% and the evening PEF by 6.2%. Terfenadine did not block the development of bronchial hyperresponsiveness. Again, terfenadine reduced symptoms while improving pulmonary function.

TABLE II. Clinical studies in asthma with cetirizine

Author	Dose	Characteristics of asthma	Comparator	Duration of study	Symptoms	Lung function	β -Agonist use
Bruttman et al ³⁵	10 mg bid	Seasonal	Placebo	2 wk	Decreased	Improved	Decreased
Bousquet et al ³⁶	10 mg and 15 mg bid	Seasonal	Terfenadine 60 mg bid	4 wk	Decreased in 15-mg group	No change	No change
Dijkman et al ³⁷	10 mg bid	Seasonal	Terfenadine 60 mg bid	3 mo	Decreased	Improved morning PEF	Decreased
Grant et al ³⁸	10 mg once daily	Seasonal	Placebo	6 wk	Decreased	No change	Decreased (not significant)
Aaronson ³⁹	20 mg once daily	Perennial	Placebo	16 wk	Decreased	No change	No change

TABLE III. Clinical studies in asthma with loratadine

Author	Dose	Characteristics of asthma	Additional drug	Duration of study	Symptoms	Lung function	β -Agonist use
Dirksen et al ⁴⁰	10 mg once daily	Moderate to severe, perennial	None	8 wk	Trend toward improvement	Trend toward improvement	Trend toward improvement
Ekstrom et al ⁴¹	20 mg once daily	Moderate to severe, perennial	None	4 wk	No change	Transient improvement	No change
Corren et al ⁴²	5 mg bid	Mild, seasonal	Pseudoephedrine 120 mg bid	6 wk	Decreased	Improved PEF	No change
Reicin et al ⁴³	20 mg once daily	Perennial	Montelukast 10 mg every day	2 wk	Decreased	Improved	Decreased

A different result was obtained when Wood-Baker et al³³ studied the effect of the addition of terfenadine 120 mg bid in 42 patients with chronic severe asthma. These subjects, mean age 50 years, had a mean FEV₁ of 53% predicted; 94% were using inhaled corticosteroids, and 41% were using theophylline. In this setting, terfenadine had no significant treatment effect on pulmonary function, symptom scores, or β -agonist use; however, nighttime awakening was reduced.

Recently, fexofenadine was studied in a 6-week trial in patients with seasonal allergic rhinitis and concurrent asthma severe enough to require treatment with inhaled corticosteroids (Table I).³⁴ At 180 mg once daily, fexofenadine resulted in a significant improvement in seasonal allergic rhinitis but only minimal improvement in home-recorded PEF and wheezing, predominantly during the first week. There were no differences for FEV₁, β -agonist use, or morning or evening total asthma symptoms. It cannot be determined whether the lack of efficacy in asthma was a result of the mild asthma in the subjects studied because of the concomitant use of inhaled steroids or because a fexofenadine dose customarily prescribed for rhinitis was used. Research is ongoing to evaluate the effects of higher-dose fexofenadine for the treatment of asthma.

Cetirizine has been evaluated in 4 separate studies in seasonal pollen asthma and in 1 study in patients with perennial asthma (Table II). In a 2-week comparison with cetirizine 10 mg bid, placebo patients had deterioration in symptoms and pulmonary function, and 23 of 28 dropped out of the study because of lack of efficacy.³⁵ In the cetirizine group, pulmonary function was maintained, symptoms improved, and only 5 of 29 withdrew from the trial.

Cetirizine has also been compared with terfenadine 60 mg bid.^{36,37} In a 4-week study, cetirizine 15 mg bid reduced symptoms of wheezing, dyspnea, and cough significantly more than either cetirizine 10 mg bid or terfenadine 60 mg bid.³⁶ In a 3-month study, cetirizine 10 mg bid was significantly more effective than terfenadine 60 mg bid in preventing asthma symptoms, improving morning peak flows, and reducing β -agonist use.³⁷

In a placebo-controlled, multicenter study during the fall pollen season,³⁸ cetirizine 10 mg per day was administered to 93 subjects, with a similar number receiving placebo. Asthma symptoms were significantly better with cetirizine for 5 of the 6 weeks of the study. There was no significant difference in spirometry and a nonsignificant reduction in β -agonist use in the cetirizine group compared with the placebo group. In addition, a small study examined the effect of 16 weeks of cetirizine, 20 mg per day, in patients with mild to moderate perennial asthma.³⁹ Compared with placebo, patients receiving cetirizine had significantly fewer asthma symptoms but no difference in pulmonary function test results.

Two studies have examined the use of loratadine alone in patients with moderate to severe asthma (Table III). In a small, crossover, steroid-tapering study, all outcomes favored loratadine 10 mg daily over placebo. However, none of the differences were significant.⁴⁰ In another crossover study in patients receiving inhaled corticosteroids, loratadine 20 mg once daily was administered for 4 weeks.⁴¹ Overall, there were no objective improvements in asthma control with loratadine compared with placebo. It was noted that the PEF was significantly higher with loratadine than placebo early in the treatment

period, but the difference progressively decreased throughout the 4 weeks of the study, suggesting a developing tolerance to the bronchodilator effect of loratadine.

In subsequent studies, loratadine has been combined with other agents (Table III). In a study in patients with mild, fall pollen asthma, loratadine 5 mg bid plus pseudoephedrine 120 mg bid was compared with placebo for 6 weeks.⁴² Total rhinitis and asthma symptom severity scores were significantly reduced in patients receiving active therapy compared with placebo throughout the 6 weeks. PEF improved significantly in the active treatment group during weeks 2 through 6. The peak effect for the combination treatment was 26 L/min compared with 9 L/min for placebo. In addition, selected measures of asthma-specific quality of life improved significantly relative to placebo.

It has been demonstrated that loratadine 10 mg bid and the leukotriene receptor antagonist zafirlukast 80 mg bid separately reduce both the early and late response to allergen challenge, but they are more effective in combination.⁴⁶ In a blinded, crossover study of patients with chronic asthma, the effect of 2 weeks' treatment with the leukotriene receptor antagonist montelukast 10 mg per day was compared with montelukast 10 mg per day plus loratadine 20 mg per day. The improvement in FEV₁ was 9.7% with montelukast alone and 13.9% with the combination ($P < .001$). In addition, mean daily β -agonist use, daytime and nighttime symptom scores, morning and evening PEFs, and patient global evaluation were all significantly better with the combination compared with montelukast alone.⁴⁴

SUMMARY

Both the first- and second-generation antihistamines have been shown to produce acute bronchodilation. The degree of improvement is greater with the second-generation antihistamines, probably because relatively larger doses can be administered without excessive drowsiness.

The reported effect of the second-generation antihistamines on the response to allergen challenge has been variable. Only terfenadine, at 3 times the conventional dose, has reduced the early and late bronchoconstrictor response. Loratadine and lower doses of terfenadine have had no effect on either the early or the late response, although loratadine did augment the effect of a leukotriene receptor antagonist on both the early and late response. Cetirizine has consistently failed to reduce the early response to allergen challenge and has generally failed to reduce the late bronchoconstrictor response; however, it has reduced the late increase in methacholine sensitivity and the influx of eosinophils in the bronchoalveolar fluid.

The results with EIB are also variable. Oral cetirizine at twice the conventional dose had no effect, whereas inhaled cetirizine reduced the exercise-induced decrease in FEV₁ by more than 50%. Astemizole at the conventional dose either reduced or delayed the decrease in FEV₁. Terfenadine, again at 3 times the normal dose, consistently reduced the decrease in FEV₁.

Several investigators have observed that the initial bronchodilator response to antihistamines does not appear to be sustained. More research is required to study this in more detail.

Three second-generation antihistamines have been studied for their clinical effect on asthma. Terfenadine was administered at 2 to 4.5 times the conventional dose to patients with mild seasonal or perennial asthma. At these doses, terfenadine improved both asthma symptoms and pulmonary function. However, when given to patients with more severe asthma, even twice the conventional dose had no effect.

Cetirizine at up to twice the conventional dose improved symptoms and pulmonary function in some patients with mild seasonal or mild to moderate perennial asthma. It has not been given to patients with severe asthma.

Loratadine, at the conventional or twice the conventional dose, showed a trend toward improvement in patients with moderate asthma but no appreciable effect in patients with more severe asthma. When combined with pseudoephedrine, conventional doses of loratadine reduced symptoms and improved pulmonary function in patients with mild seasonal asthma. When added to montelukast, twice the conventional dose of loratadine provided additional benefits in symptoms, pulmonary function, and requirement for rescue β -agonists.

CONCLUSION

There might be a role for second- and third-generation antihistamines in treating mild, and perhaps moderate, asthma. This will be most effectively achieved by administering several times the conventional dose of those drugs that are truly nonsedating, such as fexofenadine. An alternative approach would be to obtain an additive effect through combination therapy with agents such as decongestants or leukotriene receptor antagonists. This approach is particularly applicable for antihistamines that have the potential for sedation.

REFERENCES

1. Malick A, Grant JA. Antihistamines in the treatment of asthma. *Allergy* 1997;52(suppl 34):55-66.
2. Popa VT. Bronchodilating activity of an H₁ blocker, chlorpheniramine. *J Allergy Clin Immunol* 1977;55:54-63.
3. Leopold JD, Hatley JP, Smith AP. Effects of oral H₁ and H₂ receptor antagonists in asthma. *Br J Clin Pharmacol* 1979;8:249-51.
4. Hodges IG, Milner AD, Stokes GM. Bronchodilator effect of two inhaled H₁-receptor antagonists, clemastine and chlorpheniramine in wheezy school-children. *Br J Dis Chest* 1993;77:270-5.
5. Nogrady SG, Hartley JP, Handslip PD, Hurst NP. Bronchodilation after inhalation of the antihistamine clemastine. *Thorax* 1978;33:479-82.
6. Wood-Baker R, Holgate ST. The comparative actions and adverse effect profile of single doses of H₁ receptor antihistamines in the airways and skin of subjects with asthma. *J Allergy Clin Immunol* 1993;91:1005-14.
7. MacFarlane PI, Heaf DP. Selective histamine blockade in childhood asthma: the effect of terfenadine on resting bronchial tone and exercise induced bronchoconstriction. *Respir Med* 1989;83:19-24.
8. Patel KR, Ghosh SK, Matcham J. Lack of dose-response effect of terfenadine on resting bronchomotor tone in patients with asthma. *Clin Exp Allergy* 1991;21:363-6.
9. Brik A, Tashkin DP, Gong H Jr, Dauphinee B, Lee E. Effect of cetirizine,

- a new histamine H₁ antagonist, on airway dynamics and responsiveness to inhaled histamine in mild asthma. *J Allergy Clin Immunol* 1987;80:51-6.
10. Spector SL, Nicodemus CF, Corren J, Schanker HM, Rachelefsky GS, Katz RM, et al. Comparison of the bronchodilatory effects of cetirizine, albuterol and both together versus placebo in patients with mild-to-moderate asthma. *J Allergy Clin Immunol* 1995;96:174-81.
 11. Town GI, Holgate ST. Comparison of the effect of loratadine on the airway and skin responses to histamine, methacholine, and allergen in subjects with asthma. *J Allergy Clin Immunol* 1990;86:886-93.
 12. Eiser N. The effect of a beta-2-adrenergic agonist and a histamine H₁-receptor antagonist on the late asthmatic response to inhaled antigen. *Respir Med* 1991;85:393-9.
 13. Chan TB, Shelton DM, Eiser NM. Effect of an oral H₁-receptor antagonist, terfenadine, on antigen-induced asthma. *Br J Dis Chest* 1986;80:375-84.
 14. Rafferty P, Beasley R, Holgate ST. The contribution of histamine to immediate bronchoconstriction provoked by inhaled allergen and adenosine 5' monophosphate in atopic asthma. *Am Rev Respir Dis* 1987;136:369-73.
 15. Hamid M, Rafferty P, Holgate ST. The inhibitory effect of terfenadine and flurbiprofen on early and late-phase bronchoconstriction following allergen challenge in atopic asthma. *Clin Exp Allergy* 1990;20:261-7.
 16. Curzen N, Rafferty P, Holgate ST. Effects of a cyclo-oxygenase inhibitor, flurbiprofen, and an H₁ histamine receptor antagonist, terfenadine, alone and in combination on allergen induced immediate bronchoconstriction in man. *Thorax* 1987;42:946-52.
 17. Bentley AM, Walker S, Hanotte F, De Vos C, Durham SR. A comparison of the effects of oral cetirizine and inhaled beclomethasone on early and late asthmatic responses to allergen and the associated increase in airways hyperresponsiveness. *Clin Exp Allergy* 1996;26:909-17.
 18. de Bruin-Weller MS, Rijssenbeek-Nouwens LH, de Monchy JG. Lack of effect of cetirizine on early and late asthmatic response after allergen challenge. *J Allergy Clin Immunol* 1994;94:231-9.
 19. Rafferty P, Ghosh SK, deVos C, Patel KR. Effect of oral and inhaled cetirizine in allergen induced bronchoconstriction. *Clin Exp Allergy* 1993;23:528-31.
 20. Wasserfallen JB, Leuenberger P, Pecoud A. Effect of cetirizine, a new H₁ antihistamine, on the early and late allergic reactions in a bronchial provocation test with allergen. *J Allergy Clin Immunol* 1993;91:1189-97.
 21. Redier H, Chanez P, De Vos C, Rifai N, Clauzel AM, Michel FB, et al. Inhibitory effect of cetirizine on the bronchial eosinophil recruitment induced by allergen inhalation challenge in allergic patients with asthma. *J Allergy Clin Immunol* 1992;90:215-24.
 22. Gong H Jr, Tashkin DP, Dauphinee B, Djahed B, Wu TC. Effects of oral cetirizine, a selective H₁ antagonist, on allergen- and exercise-induced bronchoconstriction in subjects with asthma. *J Allergy Clin Immunol* 1990;85:632-41.
 23. Hartley JP, Nogrady SG. Effect of an inhaled antihistamine on exercise-induced asthma. *Thorax* 1980;35:675-9.
 24. Ghosh SK, De Vos C, McLroy I, Patel KR. Effect of cetirizine on exercise induced asthma. *Thorax* 1991;46:242-4.
 25. Clee MD, Ingram CG, Reid PC, Robertson AS. The effect of astemizole on exercise-induced asthma. *Br J Dis Chest* 1984;78:180-3.
 26. Backer V, Bach-Mortensen N, Becker U, Brink L, Howitz P, Hanse KK, et al. The effect of astemizole on bronchial hyperresponsiveness and exercise-induced asthma in children. *Allergy* 1989;44:209-13.
 27. Finnerty JP, Holgate ST. The contribution of histamine release and vagal reflexes, alone and in combination, to exercise-induced asthma. *Eur Respir J* 1993;6:1132-7.
 28. Finnerty JP, Holgate ST. Evidence for the roles of histamine and prostaglandins as mediators in exercise-induced asthma: the inhibitory effect of terfenadine and flurbiprofen alone and in combination. *Eur Respir J* 1990;3:540-7.
 29. Howarth PH. Histamine and asthma: an appraisal based on specific H₁-receptor antagonism. *Clin Exp Allergy* 1990;21(suppl 2):31-41.
 30. Meltzer EO. Pharmacological treatment options for allergic rhinitis and asthma. *Clin Exp Allergy* 1998;28(suppl 2):27-36.
 31. Taytard A, Beaumont D, Pujet PC, Sapene M, Lewis PJ. Treatment of bronchial asthma with terfenadine: a randomized controlled trial. *Br J Clin Pharmacol* 1987;24:743-6.
 32. Rafferty P, Jackson L, Smith R, Holgate ST. Terfenadine, a potent histamine H₁-receptor antagonist in the treatment of grass pollen sensitive asthma. *Br J Clin Pharmacol* 1990;30:229-35.
 33. Wood-Baker R, Smith R, Holgate ST. A double-blind, placebo controlled study of the effect of the specific histamine H₁-receptor antagonist, terfenadine, in chronic severe asthma. *Br J Clin Pharmacol* 1995;39:371-5.
 34. Kaliner M, Gottlieb G, Lieberman A, Finn A, Charous BL, Walds J, et al. Safety of fexofenadine HCl in asthmatic patients requiring inhaled corticosteroids in accordance with NHLBI guidelines [abstract]. *J Allergy Clin Immunol* 2000;1:S388.
 35. Bruttman G, Pedrali P, Arendt C, Rihoux JP. Protective effect of cetirizine in patients suffering from pollen asthma. *Ann Allergy* 1990;64:224-8.
 36. Bousquet J, Emonot A, Germouty J, Molina C, Montane F, Perrin-Fayolle M, et al. Double-blind multicenter study of cetirizine in grass-pollen-induced asthma. *Ann Allergy* 1990;65:504-8.
 37. Dijkman JH, Hekking PR, Molkenboer JF, Nierop G, Vanderschueren R, Bernheim J, et al. Prophylactic treatment of grass pollen-induced asthma with cetirizine. *Clin Exp Allergy* 1990;20:483-90.
 38. Grant JA, Nicodemus DF, Findlay SR, Glovsky MM, Grossman J, Kaiser H, et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1995;95:923-32.
 39. Aaronson DW. Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. *Ann Allergy Asthma Immunol* 1996;76:440-6.
 40. Dirksen A, Engel T, Frolung L, Heinig JH, Svendsen SUG, Weeke B. Effect of a non-sedative antihistaminic (loratadine) in moderate asthma: a double-blind controlled clinical crossover trial. *Allergy* 1989;44:566-71.
 41. Ekstrom T, Osterman K, Zetterstrom O. Lack of effect of loratadine on moderate to severe asthma. *Ann Allergy Asthma Immunol* 1995;75:287-9.
 42. Corren J, Harris AG, Aaronson D, Beaucher W, Berkowitz R, Bronsky E, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. *J Allergy Clin Immunol* 1997;100:781-8.
 43. Roquet A, Dahlen B, Kumlin M, Ihre E, Anstren G, Binks S, et al. Combined antagonism of leukotrienes and histamine produces predominant inhibition of allergen-induced early and late phase airway obstruction in asthmatics. *Am J Respir Crit Care Med* 1997;155:1856-63.
 44. Reicin A, White R, Weinstein SF, Finn AF Jr, Nguyen H, Peszek I, et al. Montelukast, a leukotriene receptor antagonist, in combination with loratadine, a histamine receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med* 2000;160:2481-8.