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REFERENCES

1. Munir AKM, Einarsson R, Kjellman N-IM, Björkstén B. Mite (*Der p 1*, *Der f 1*) and cat (*Fel d 1*) allergens in homes of babies with a family history of allergy. *Allergy* 1993;48:158-63.
2. Wickman M, Nordvall SL, Pershagen G, Sundell J, Schwartz B. House dust sensitization in children and residential characteristics in a temperate region. *J ALLERGY CLIN IMMUNOL* 1991;88:89-95.
3. Lau S, Falkenhurst G, Weber A, et al. High mite-allergen exposure increases the risk of sensitization in atopic children and young adults. *J ALLERGY CLIN IMMUNOL* 1989;84:718-25.
4. Munir AKM. Exposure to indoor allergens and relation to sensitization and asthma in children. Linköping, Sweden: Linköping University Medical Dissertations, 1994;412:1-89.
5. Munir AKM, Björkstén B, Einarsson R, Ekstrand-Tobin A, Warner A, Kjellman N-IM. Mite allergens in relation to home conditions and sensitization of asthmatic children from three climatic regions. *Allergy* 1995;50:55-64.
6. Platts-Mills TAE, Thomas WR, Aalberse RC, Vervloet D, Chapman MD. Dust mite allergens and asthma: report of the second international workshop. *J ALLERGY CLIN IMMUNOL* 1992;89:1046-60.
7. Platts-Mills TAE, Tovey ER, Mitchell EB, Moszoro H, Nock P, Wilkins SR. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet* 1982;2:675-8.
8. Munir AKM, Einarsson R, Schou C, Dreborg SKG. Allergens in school dust. I. The amount of the major cat (*Fel d 1*) and dog (*Can f 1*) allergens in dust from Swedish schools is high enough to probably cause perennial symptoms in most children with asthma who are sensitized to cat and dog. *J ALLERGY CLIN IMMUNOL* 1993;91:1067-74.
9. Dybendal T, Elsayed S. Dust from carpeted and smooth floors. V. Cat (*Fel d 1*) and mite (*Der p 1* and *Der f 1*) allergen levels in school dust. Demonstration of the basophil histamine release induced by dust from classrooms. *Clin Exp Allergy* 1993;22:1100-6.
10. Wood RA, Egglestone PA, Lind P, et al. Antigenic analysis of house dust samples. *Am Rev Respir Dis* 1988;137:358-63.

Adverse effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors associated with elevated serum IgE and eosinophilia

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The major reported adverse reactions to the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, lovastatin and pravastatin, are myopathy (0.5% to 1.9%) and increased liver transaminases (2%). Both reactions are reversible when drug therapy is discontinued. Other reported, drug-attributable consequences are insomnia, gastrointestinal symptoms, and skin rash.^{1,2} In the EXCEL (Expanded Clinical Evalu-

Abbreviation used

HMG-CoA: 3-Hydroxy-3-methylglutaryl coenzyme A

ation of Lovastatin) study, adverse experiences were reported as possibly, probably, or definitely drug-related in approximately 0.5% to 1.0% of patients in any drug-treated group.³ Only three cases of skin rash were reported in patients receiving lovastatin. In another study, Tobert et al.⁴ noted that an erythematous eruption developed in one of 24 subjects after 2 days of treatment with 15 mg lovastatin but disappeared despite drug continuation. These authors also reported that two of 59 subjects experienced maculopapular rash while receiving lovastatin.⁵ No reports of hypersen-

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sitivity reactions associated with respiratory difficulty, elevation in serum IgE concentration, or elevated eosinophil counts have been found in patients receiving HMG-CoA reductase inhibitors (lovastatin, pravastatin). In addition, although both formulations of inhibitor show significant structural homology, no cross-reactivity of immunologic adverse reactions has been reported. We report a case of a hypersensitivity reaction to HMG-CoA reductase inhibitors manifested by airway hyperactivity, elevated serum IgE concentration, and eosinophilia; the reaction appeared to be cross-reactive between two different formulations.

CASE REPORT

A 70-year-old man, with no known cardiopulmonary disease who had been accustomed to a daily regimen of 1 to 2 miles of jogging and 7 miles of walking on a treadmill, was referred to the University of Michigan Allergy Clinic in February 1992 for evaluation of possible mold allergy because of the onset of asthma-like symptoms (wheezing, dyspnea on exertion), which had persisted for 1 year. Symptoms also included one episode of acute facial angioedema, which required emergency department intervention and treatment with a short course of corticosteroid (in September 1991). The patient also noted fatigue and a 6-month history of Raynaud's phenomenon involving the third and the fourth fingers of both hands. Evaluation elsewhere (from September 1991 to January 1992) revealed normal electrocardiogram and stress thallium test results and normal thyroid function. From January 1992 to February 1992, laboratory findings demonstrated an elevated Westergren sedimentation rate, elevated serum IgE, and peripheral blood eosinophilia (Fig. 1, A). Prominent ("dirty") interstitial markings were noted on chest roentgenogram, and a 25% decrease in forced expiratory volume in 1 second/forced vital capacity (baseline value = 3.19/4.15 L) was noted to have occurred over the previous year. Since an initial evaluation by a pulmonologist (in January 1992), the patient had been treated with inhaled triamcinolone acetonide and albuterol sulfate for the asthma-like symptoms; however, he was still unable to carry out his usual exercise routine because of dyspnea on exertion accompanied by chest pressure.

In February 1992, evaluation in our clinic confirmed the elevated serum IgE (1300 IU/ml; reference ranges, 0 to 158 IU/ml) and the eosinophilia (5200/mm³, 48% of differential count). Results of immediate skin tests to pollens, dust mites, and molds were negative. Also, stool cultures for ova and parasites were negative on three occasions. The creatine kinase and transaminase levels were within normal limits. Medication profile at the time of evaluation was: lovastatin, dipyridamole, aspirin, multivitamins, vitamin C, vitamin E (all since late 1990), and terfenadine (since September 1991), in addition to the triamcinolone acetonide and albuterol sulfate inhalers.

After the initial assessment in the allergy clinic, the patient was instructed to stop taking all medications. Within 2 months, respiratory symptoms completely resolved, and serum IgE level and peripheral blood eosinophil count returned to the normal range (Fig. 1, A). Subsequently, lovastatin alone was restarted for treatment of persistently elevated serum cholesterol (ranging from 240 to 295 mg/dl). Two months after lovastatin was restarted, asthma-like symptoms (wheezing, dyspnea on exertion) recurred, with an associated elevation of IgE level (500 IU/ml). Lovastatin was discontinued when the IgE level rose to 950 IU/ml; thereafter, the patient's clinical symptoms improved and completely resolved, and the serum IgE level again approached normal (200 IU/ml) 2 months later. Because of the patient's concern about his continuing high serum cholesterol level (262 mg/dl), pravastatin therapy was initiated 2½ months after lovastatin was discontinued. The patient's serum IgE level progressively increased (from 250 to 800 IU/ml), and after taking pravastatin for 6 months, the patient experienced urticaria (Fig. 1, A). Pravastatin was discontinued and hydroxyzine hydrochloride treatment was initiated to relieve his symptoms. However, the patient's serum IgE level (600 IU/ml) remained persistently elevated, and diffuse urticaria plus mild respiratory symptoms (nasal congestion, throat irritation, and wheezing with exertion) continued for 8 weeks. These symptoms responded to a short course of oral steroids (prednisone 50 mg daily tapered to 10 mg daily over 3 weeks). Subsequently, urticaria and respiratory symptoms resolved at the end of a 3-week course of steroid treatment, and the serum IgE level declined to 250 IU/ml (Fig. 1, A). The patient has continued to be free of symptoms, with a normal serum IgE level, since July 1993.

DISCUSSION

We report presumptive hypersensitivity reactions to two different formulations of HMG-CoA reductase inhibitors. These reactions were manifested by angioedema, respiratory difficulty, Raynaud's phenomenon, and urticaria associated with an elevated serum IgE level. All of the symptoms and laboratory abnormalities resolved after discontinuation of the medications and recurred on rechallenge. Although no measure of specific immune reactivity to these drugs was performed, the cause-effect relationship was strongly supported by the recurrence of the symptoms and the elevation of total serum IgE level after medication was reintroduced. Generalized elevations of serum IgE level, as a result of drug treatment, with signs and symptoms ranging from pruritus or urticaria to severe asthma or anaphylaxis, are also well described in adverse reactions to other agents. It is unclear, in this case, whether the HMG-CoA reductase inhibitors induced a drug-specific IgE-antibody response or the overall elevations of IgE

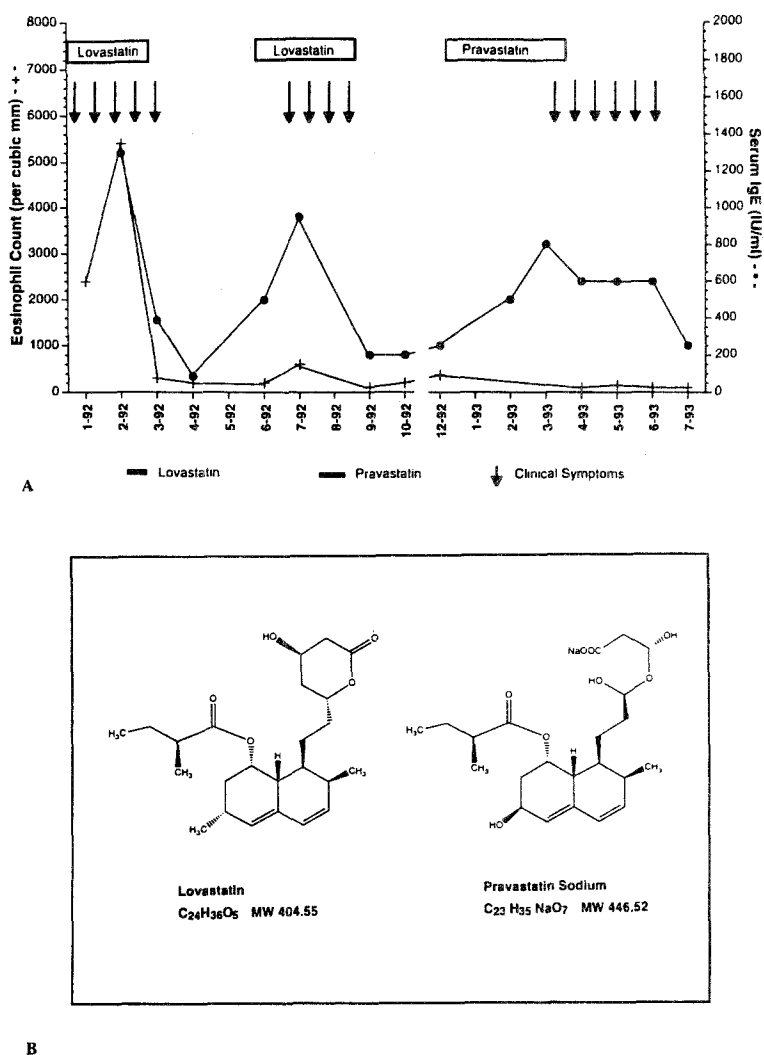


FIG. 1. A, Serum IgE, peripheral blood eosinophil count, and clinical symptoms associated with HMG-CoA reductase inhibitor treatment course. B, Structure of lovastatin and pravastatin. All contain the naphthalenyl structure.

antibody were induced through nonspecific alteration in cytokines generated by the immune response to the drugs, their metabolites, or a pharmacologic effect of the drug. Unfortunately, reliable means to assay for specific IgE antibodies against the HMG-CoA reductase inhibitors are not currently available.

In conclusion, we have described an individual with hypersensitivity reactions to two formulations of HMG-CoA reductase inhibitors, which have similar frame naphthalenyl structures but different side chains (Fig. 1, B). Because of the very common use of these drugs and the apparent structural homology between their formulations, it is important for physicians to be aware that such reactions can occur during therapy.

REFERENCES

1. Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. *Am J Cardiol* 1988;62:28J-34J.
2. Smellie WAS, Lorimer AR. Adverse effects of lipid-lowering drugs. *Adverse Drug React Toxicol Rev* 1992;11:71-92.
3. Bradford RH, Shear CL, Chremos AN, et al. Expanded clinical evaluation lovastatin (EXCEL) study results. *Arch Intern Med* 1991;151:43-9.
4. Tobert JA, Hitzenger G, Kukovetz WR, Holmes IB, Jones KH. Rapid and substantial lowering of human serum cholesterol by Mevinolin (MK-803), an inhibitor of hydroxymethylglutaryl-coenzyme A reductase. *Atherosclerosis* 1982;41:61-5.
5. Tobert JA, Bell GD, Birtwell J, et al. Cholesterol-lowering effect of Mevinolin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, in healthy volunteers. *J Clin Invest* 1982;69:913-9.