Correspondence

Bone Loss and Inhaled Glucocorticoids

To the Editor: The study by Israel et al. (Sept. 27 issue)[1] of bone thinning in women with asthma did not effectively control for the critical variables of the level of physical activity and the severity of asthma.

Comparisons between patients with mild asthma and those with persistent asthma who are receiving high doses of inhaled glucocorticoids must include a careful evaluation of base-line characteristics.[2] Table 2 of the article shows that the 28 women who did not use inhaled glucocorticoids weighed less than the 42 women who required more than eight puffs of inhaled glucocorticoids per day (mean [±SD], 140±20 vs. 154±40 lb), had nearly twice the level of physical activity (98±54 vs. 55±71 metabolic hours per week), had a lower incidence of past or current use of inhaled glucocorticoids (14±36 percent vs. 62±49 percent), and were less likely to have a history of oral-glucocorticoid use (36± 49 percent vs. 79±42 percent). All of these base-line differences appear to be statistically significant. It is as if we compared the bones of a busload of women soccer players with those of a busload of sedentary women.

A relative lack of gravitational exercise can obviously contribute to bone loss, as shown most clearly in astronauts returning from zero gravity. Because the presence of persistent asthma limits one's ability to exercise, the resulting inactivity and other changes in variables reflecting the severity of asthma (e.g., weight, prednisone use, and airway inflammation) invalidate any reliable analysis of the effects of inhaled glucocorticoids on bone loss in groups that were so dissimilar at base line in the absence of a randomized scheme of treatment allocation.

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2. Kaiser DL. Statistical concepts in infection control. In: Wenzel RP, ed. Prevention and control of nosocomial infections. Baltimore: Williams & Wilkins, 1987:591-600.

To the Editor: Israel et al. observed a dose-related decline in bone density at the hip among users of inhaled glucocorticoids. We conducted a large cohort study and found a dose-related increase in the risk of fracture among adult users of inhaled glucocorticoids.[1] However, patients who used bronchodilator drugs had similar degrees of risk. Our conclusion was that this excess risk is more likely to be related to the presence of underlying respiratory disease than to treatment.

Israel et al. found that pulmonary function was similar among the three groups and inferred that there was no confounding related to differences in the severity of asthma. Since treatment was not randomly assigned, the high-dose group most likely had more severe asthma. Despite having similar pulmonary function, more patients in the high-dose group than in the other groups were excluded because they had received more than 30 days of oral or parenteral glucocorticoid therapy. Inhaled glucocorticoids can suppress the symptoms of bronchoconstriction, but they do not cure the disease. Their effects on the natural history of asthma are not clearly understood.[2] Complications may thus occur independently of the level of bronchoconstriction.

The bone loss associated with the use of oral glucocorticoids is principally trabecular, with a greater loss in the lumbar spine and less of a loss in the proximal femur. The spine is associated with the largest increases in the risk of fracture.[3] The pattern of effect on bone density at the spine and hip reported by Israel et al. does not support the hypothesis that inhaled glucocorticoids influence bone in a fashion similar to that of oral glucocorticoids.

We agree that patients using inhaled glucocorticoids have

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an increased risk of fracture. The potential role of asthma in increasing this risk should not be underestimated.

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To the Editor: Israel et al. report that inhaled glucocorticoids lead to a dose-related decline in bone density at the hip in premenopausal women. However, the authors never comment on the control group in the study, which was not exposed to glucocorticoids. The loss of bone mineral density in women older than 25 years of age is well documented, and Israel et al. have given us no means of distinguishing physiologic changes from those resulting from medication.

That there is a normal decline in bone mineral density with age also calls into question the data from the study's bone densitometers. Data from the femoral neck and lumbar spine do not correspond to the expected base-line loss of 0.7 percent per year.[1] Such measuring error calls into question the small changes in density that Israel et al. report as statistically significant. More analysis of the control group and more data are necessary to understand the consequences of this widespread treatment approach.

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The authors reply:

To the Editor: In response to Dr. Kerwin: the "busloads" of women we compared were well matched. There were no statistically significant differences among the groups in weight or the level of physical activity. The apparent difference in the level of physical activity was due to a typographical error in Table 2. The mean level of physical activity in the group of women who did not take inhaled glucocorticoids was 48 metabolic hours per week, not 98. In addition, analyses that also adjusted for weight and level of physical activity did not affect our quantitative conclusions about the dose-related loss in bone density at the hip and trochanter.

Naturally, our groups differed with respect to the use of inhaled glucocorticoids. This was the independent variable used to assemble the groups. We also expected the incidence of a history of oral-glucocorticoid use before the study to differ among the groups. However, the data obtained during the study were not confounded by the use of oral glucocorticoids, which was prospectively monitored; we performed an a priori analysis that was restricted to patients who did not receive oral glucocorticoids during the study. Furthermore, data from van Staa et al.,[1] among others, suggest that the presence of a history of glucocorticoid use before the study was unlikely to affect our outcome, since there is a rapid offset of the effects of oral glucocorticoids on bone density once therapy is stopped.

Since we did not examine any patients without asthma, we cannot confirm the observation of van Staa et al. regarding bronchodilator users and controls. However, when van Staa and colleagues compared users of high-dose inhaled glucocorticoids with those who used bronchodilators alone (an analysis similar to ours), their findings were remarkably similar to ours.[2] They observed an increased rate of hip fracture with the use of high-dose inhaled glucocorticoids. The rate was not a function of the underlying population, since it declined toward base line once the treatment was discontinued. Furthermore, there was an increased rate of hip fracture and not of spinal fracture. Why inhaled glucocorticoids produce a pattern of accelerating bone loss that differs from that reported with oral glucocorticoids is unclear.

Dr. Glazer misunderstands our analysis. Patients who did not use inhaled glucocorticoids were very much part of the analysis (as indicated by the points superimposed on the ordinate in each panel of Figure 2 of our article). In fact, the yearly decline in bone density per puff of inhaled glucocorticoid that we report is the supplementary decline, which would occur in addition to any physiologic change in bone density that would be occurring in the group that was not using inhaled glucocorticoids. We used a very precise technique for measuring bone mass — dual x-ray absorptiometry — and the results were interpreted by one observer. However, as we noted in the article, on the basis of the results of dietary screening, patients received supplemental calcium, vitamin D, or both. This supplementation may have influenced the yearly rate of bone loss in our subjects, including the rate in the group that did not use inhaled glucocorticoids. Nonetheless, we found that inhaled glucocorticoids were associated with a dose-related decrease in bone density that was superimposed on any positive effect that may have resulted from dietary supplementation.

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Urinary Tract Infections and a Multidrug-Resistant *Escherichia coli* Clonal Group

To the Editor: The report by Manges et al. (Oct. 4 issue)[1] regarding the widespread distribution of multidrug-resistant *Escherichia coli* is both important and timely. We have found even higher rates of resistance to trimethoprim–sulfamethoxazole (TMP-SMX) among *E. coli* and other organisms at Elmhurst Hospital in Queens, New York. This hospital serves an incredibly diverse immigrant population that includes large numbers of people from Asia and Latin America. As part of a quality-improvement project, we reviewed more than 900 positive urine cultures that had been obtained since October 1998; approximately 40 percent were resistant to TMP-SMX. The majority of our urine cultures grew *E. coli* with patterns of resistance that were similar to those reported by Manges et al.

Our data also show that about 15 percent of the cultures with minimal resistance to ciprofloxacin were resistant to cephalexin. Ciprofloxacin would seem to be a good choice, but since the World Trade Center tragedy and the anthrax scare, there has been a shortage of ciprofloxacin. Even if the supply of ciprofloxacin were not in question, the cost of treatment with this drug is often prohibitive for indigent, uninsured patients.

Are the authors aware of high levels of resistance in other urban or immigrant populations? What alternatives do they suggest for effective empirical treatment of urinary tract infections at a reasonable cost?

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1. Manges AR, Johnson JR, Foxman B, O'Bryan TT, Fullerton KE, Riley LW. Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. N Engl J Med 2001;345:1007-13.

To the Editor: Manges et al. reported finding a clonal strain of *E. coli* that was responsible for urinary tract infections in women in three states between 1996 and 2000. Is this strain responsible for cases of outpatient urinary tract infections in other geographic areas?[1]

We examined 213 isolates of *E. coli* from urine cultures obtained in 1998 from patients — 85 percent of whom were outpatients and 84 percent of whom were women — to investigate the incidence of antibiotic-resistant strains at Cook County Hospital in Chicago.[2] Our findings were similar to those of Manges et al.; 24 percent of isolates were resistant to TMP-SMX. However, using the same method of pulsed-field gel electrophoresis[3] used by Manges et al., we found that our TMP-SMX–resistant isolates were distinct, unrelated strains. Hence, epidemic spread of a single *E. coli* clone could not explain the high prevalence of resistance to TMP-SMX in urinary isolates in Chicago, although the spread of a common resistance element is conceivable.

Our chart review suggested an alternative hypothesis: 68 percent of the patients had Hispanic surnames. In contrast, only 20 to 30 percent of our outpatient population is Hispanic. Recent travel to or acquisition of TMP-SMX from Mexico or other Latin American countries, where the use of antibiotics is unrestricted, may have contributed to the incidence of TMP-SMX–resistant isolates at our facility. International travel and Hispanic ethnic background were predictors of infection with TMP-SMX–resistant strains in another study of urinary tract infections with *E. coli*.[4] Although Manges et al. do not report their patients' race or ethnic group, their infections and any antecedent antibiotic treatments may have been more likely than those in our patients to have been acquired locally.

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To the Editor: Manges et al. describe an epidemic of antibiotic-resistant *E. coli* urinary tract infections in women, stating that contaminated food may have been the culprit. Much of the antibiotics used in this country are given to food animals.

To date, the concern about infections with antibiotic-resistant food-borne pathogens has focused on salmonella[1,2] and campylobacter.[3] However, food-borne strains of resistant *E. coli* also infect people, either through direct colonization with resistant strains from animals or through the transfer of drug-resistance plasmids from salmonella or *E. coli* in animals to *E. coli* in people.[4] The next logical step in understanding the findings of Manges et al. would be to screen *E. coli* isolates from food animals to determine whether a related strain is present. The finding of a similar strain would be compelling evidence that antibiotic use in animals poses a widespread threat to the nearly 8 million women who

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have urinary tract infections each year. It would also provide additional scientific data to support actions by the Food and Drug Administration or Congress to phase out the use of medically important antibiotics in livestock and poultry.

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The authors reply:

To the Editor: The prevalence of antibiotic resistance among *E. coli* causing urinary tract infections varies geographically for reasons that are poorly understood.[1] Ethnic background has received little attention to date as a predictor of antibiotic resistance in uropathogenic *E. coli,* so the findings described by Dr. Sandel and colleagues and by Dr. Petrof and colleagues suggest a need for further research. It is probable that some resistant strains are imported into the United States, as indicated by the emergence of TMP-SMX–resistant fecal *E. coli* among tourists who have taken this agent prophylactically while visiting Mexico.[2]

Multidrug-resistant salmonella infections in the United States were found to be associated with Hispanic surnames.[3] In the case of enteric pathogens, such an association could have several possible explanations: resistant organisms may be imported from areas with a high prevalence of resistance, differences in antibiotic use among different populations in the United States may predispose users to acquire multidrug-resistant strains,[3] and cultural or ethnic differences in diet may contribute to an increased risk of exposures to some types of foods contaminated with resistant organisms.[4] In any case, we strongly agree with Drs. Barlam and Moellering that the use of antibiotics as growth promoters in animal feed is a major contributor to the emergence of multidrug-resistant food-borne pathogens and that there is no reason to believe that this situation applies only to traditional enteric organisms, such as salmonella and campylobacter.

Finally, to address the important questions posed by Sandel and colleagues, oral alternatives to TMP-SMX for the treatment of urinary tract infections with TMP-SMX–resistant *E. coli* include ciprofloxacin and other fluoroquinolones, nitrofurantoin, fosfomycin tromethamine, amoxicillin–clavulanate, and extended-spectrum cephalosporins.[1,5] Of these, the fluoroquinolones would probably be the most effective, whereas nitrofurantoin would be the least expensive.[5] However, nitrofurantoin must be given for more than three days, even in cases of cystitis,[5] and is not useful for the treatment of pyelonephritis.

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Polymorphisms of the β_2-Adrenergic Receptor

To the Editor: Dishy et al. (Oct. 4 issue)[1] report that polymorphisms of the β_2-adrenergic receptor influence agonist-promoted desensitization of β_2-adrenergic receptor–mediated vasodilatation. Desensitization can be an important homeostatic event but may also limit the therapeutic effectiveness of agonists (a response called tachyphylaxis). The authors indicate that their findings were unexpected, given results of in vitro studies in which my colleagues and I used polymorphic β_2-adrenergic receptors that were expressed in cells in either recombinant[2] or native[3] form. However, the effect of polymorphisms in vivo is dependent on whether receptors are under static or dynamic regulation. The concept (Fig. 1) is broadly applicable and is important to consider, since the number of polymorphic genes studied in cell-based systems and humans will undoubtedly increase during the next few years.[4] With static regulation, the typically low levels of endogenous agonists (catecholamines) do not appreciably desensitize receptors under normal circumstances in vivo. Thus, the altered regulatory activities, such as desensitization, that result from a polymorphism are observed only after treatment with an exogenous agonist. In contrast, with dynamic regulation, receptors are also constantly regulated by their endogenous agonists, so that highly sensitive polymorphic receptors are "pre-desensitized" before the challenge of an exogenous agonist is presented. Such receptors might not become further desensitized with the persistent presence of an exogenous agonist, thereby revealing an apparently paradoxical phenotype.

The results of Dishy et al. are partially consistent with our in vitro studies if one considers the dynamic model: persons

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Single-Nucleotide Polymorphism	In Vitro Phenotype	Effect of Endogenous Agonist	In Vivo Response: Initial	In Vivo Response: After desensitization	Tachyphylaxis
Static model					
Polymorphism A	Moderate down-regulation	None			Moderate
Polymorphism B	Maximal down-regulation	None			Maximal
Dynamic model					
Polymorphism A	Moderate down-regulation	Moderate down-regulation			Moderate
Polymorphism B	Maximal down-regulation	Maximal down-regulation			None

Figure 1. Static and Dynamic Models of the Regulation of Polymorphic Receptors.

Receptors with single-nucleotide polymorphisms and their in vitro and in vivo properties are shown. The in vivo responses before and after a desensitization challenge are shown as bar graphs with arbitrary units. The paradoxical lack of in vivo desensitization in the receptor with polymorphism B, which has enhanced down-regulation in vitro, is apparent in the dynamic model.

with a substitution of glycine for arginine at position 16 (Gly16) do not have desensitization, yet in vitro this receptor has enhanced down-regulation; on the other hand, persons with the wild-type allele, Arg16, have desensitization in vivo, but there is less down-regulation of this receptor in vitro.[2] A similar finding has been reported in patients with asthma: patients who are homozygous for Arg16, but not those who are homozygous for Gly16, have tachyphylaxis to regularly scheduled albuterol.[5] These issues also highlight the necessity of both clinical and basic studies to delineate the physiological consequences and molecular mechanisms of clinically relevant polymorphisms.

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1. Dishy V, Sofowora GG, Xie H-G, et al. The effect of common polymorphisms of the β_2-adrenergic receptor on agonist-mediated vascular desensitization. N Engl J Med 2001;345:1030-5.
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The authors reply:

To the Editor: We are grateful to Dr. Liggett for his comments. In fact, we have previously shown that β_2-adrenergic receptors are indeed dynamically regulated by endogenous catecholamines in vivo,[1,2] and therefore we had considered his suggestion — that persons with the Gly16 variant of the β_2-adrenergic receptor, which has enhanced down-regulation in vitro, did not have further tachyphylaxis in vivo because they were already desensitized in response to endogenous catecholamines. Although we could not definitively exclude the possibility that the Gly16 variants were already desensitized, we thought it unlikely because, as shown in Table 2 of our article, the initial responses to isoproterenol in subjects who were homozygous for Arg16 or Gly16 (but matched for glutamine at position 27 [Gln27]) did not differ, whereas as illustrated in the bottom panel of Dr. Liggett's figure, preexisting desensitization in subjects homozygous for Gly16 should result in a decreased initial response to an agonist. Other factors that may account for differences between studies of adrenergic-receptor regulation performed in vitro and in vivo include different concentrations and duration of agonist exposure and modulation of responses by other genetic or homeostatic mechanisms. We agree that our findings illustrate the critical importance of studying the functional effects of genetic variations in vivo as well as in vitro.

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nist interactions by physiological changes in circulating catecholamines. J Clin Invest 1983;72:164-70.

B-Cell Deficiency and Type 1 Diabetes

To the Editor: Martin and colleagues (Oct. 4 issue)[1] report a case of type 1 diabetes mellitus in a patient with profound B-cell deficiency. It is now clear that B-cell–deficient nonobese diabetic (NOD) mice exhibit profound resistance to spontaneous autoimmune diabetes.[2-4] Indeed, several studies have indicated that the antigen-presenting role of B cells is crucial for the activation of diabetogenic T cells.[3] Recently, detailed characterization of B-cell–deficient NOD mice[5] showed that, despite their resistance to spontaneous autoimmune diabetes, these mice are susceptible to mild insulitis and, on treatment with cyclophosphamide, are susceptible to the development of diabetes.

These findings led us to conclude that in NOD mice, B lymphocytes are required for overcoming a checkpoint in the spontaneous evolution of autoimmune diabetes.[3] Our studies indicate that islet beta cells are targeted in the absence of B lymphocytes and that, given appropriate environmental provocation, B-cell–deficient NOD mice retain the potential for developing autoimmune diabetes. In the absence of a careful epidemiologic analysis of B-cell–deficient patients who harbor a genetic susceptibility to type 1 diabetes mellitus, it is premature to conclude that B cells and autoantibodies are irrelevant to the pathogenesis of this autoimmune disease in humans.

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To the Editor: Martin et al. demonstrate convincingly that autoimmune type 1 diabetes can occur in the absence of humoral immunity. Their report raises the question of whether more common, less severe defects in humoral immunity represent risk factors of type 1 diabetes. There is evidence that clinically apparent common variable immunodeficiency may be more common in children with early-onset disease than in other children.[1] It is possible that common variable immunodeficiency may also occur in older persons with type 1 diabetes.[2,3] The underlying genetic abnormalities in this type of immunodeficiency are probably heterogeneous and less than completely understood.[4-6]

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The authors reply:

To the Editor: In response to our report that neither B cells nor autoantibodies are critically required for the development of type 1 diabetes, Noorchashm and colleagues argue that B cells are required to overcome a checkpoint in the development of diabetes in the NOD-mouse model, and they provide evidence that islet-cell autoimmunity can arise in the absence of B cells. We agree that it is conceivable that B cells and autoantibodies contribute to the development of disease.[1] Nonetheless, the important message of our study is proof of principle, since in our patient type 1 diabetes clearly developed in the absence of B cells. General relevance is suggested by the fact that the patient carried the HLA alleles known to be strongly associated with type 1 diabetes.[2] Interestingly, NOD mice have a similar, critical major-histocompatibility-complex–associated genetic predisposition to autoimmune diabetes.[2] In fact, in NOD mice B cells are not an absolute requirement for the development of diabetes.[3] An important remaining difference between autoimmune diabetes in NOD mice and type 1 diabetes in humans is the presence of autoantibodies against the islet autoantigens glutamic acid decarboxylase and IA-2, which serve as important predictors of type 1 diabetes, in humans, although the diseases in mice and humans share autoantibodies against insulin.[4]

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The Acts of Terrorism

To the Editor: People all over the world were shocked by the disaster of September 11, 2001. I want to emphasize what the editors wrote about medical insurance in the *Journal*'s editorial on the subject (Oct. 11 issue)[1]: "Victims and their families must receive medical and mental health attention regardless of their ability to pay and whether or not they have medical insurance."

I believe that the international community of physicians should fight for justice in medical treatment. It is noteworthy that 40 million Americans have no medical insurance and billions of people in the Third World do not receive basic medical treatment. Physicians may not be able to save the world, but our united voice must be heard loud and clear. Everybody on this planet deserves medical and mental health care, regardless of his or her ability to pay. Justice in medical care might help to prevent hatred and frustration. Justice in medical care will not solve the problem of terrorism, but it might play a part in preventing it.

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1. The Editors. September 11, 2001. N Engl J Med 2001;345:1126.

To the Editor: The editorials on bioterrorism (July 26 issue[1] and Oct. 11 issue) called for an improved national program of preparedness, including a strengthened public-service infrastructure, improvements in diagnosis, better integration of information, and timely reporting of laboratory results. An important omission in these proposals is the role of the nation's 17,000 nursing homes as a necessary addition to the evolving system of response. There are 1,600,000 nursing home beds, of which approximately 200,000 are unoccupied on any given day.[2] The nursing homes have about twice the total number of beds that hospitals have, are located in every community in the United States, employ skilled nursing staffs and medical directors, and are linked with other medical staffs in the community. They also have established mechanisms for rehabilitation, laboratory testing, radiology, and the transportation of patients. Moreover, family and social-service support are part of the work of nursing homes.

With a small amount of additional effort and planning, the nursing homes can enhance the developing response to natural or man-made emergencies. A beneficial byproduct will be a strengthening of the nursing homes in each community and improvement in their performance of their traditional role. Fear of terrorism is understandable, but fear of the nursing home is not an acceptable reason to overlook this opportunity to enhance our response to these threats to the public.

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To the Editor: The same species that eradicated smallpox and has very nearly eradicated poliomyelitis has also committed innumerable acts of violence against itself. Will we ever learn that every war is a civil war?

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The editors reply:

The new threats of massive terrorism have developed amid the anger and resentment that have been building in oppressive, failing countries that do not provide for the basic needs of their people. Dr. Rokach's statement is a reminder that any plan to counter the underlying causes of terrorism should include plans to improve the health of those trapped in severe poverty. The health care resources of the economically developed countries are enormous. Some small fraction of those resources could produce substantial improvements for those living in the poorest countries.

In the aftermath of September 11 and the subsequent acts of biologic terrorism, we know that preparedness is now required for responses to acts that once seemed unimaginable. Those responses should draw on all our health care resources, including nursing homes and their personnel, as Dr. Libow points out. As Dr. Libow also suggests, being forced to create such contingency plans could result in the development of a better perspective on some of the problems in the fragmented health care system of the United States.

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JEFFREY M. DRAZEN, M.D.

Cerivastatin and Reports of Fatal Rhabdomyolysis

To the Editor: Bayer's voluntary withdrawal of cerivastatin from the U.S. market led to questions regarding the safety of all hydroxymethylglutaryl–coenzyme A reductase inhibitors,

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TABLE 1. REPORTED CASES OF FATAL RHABDOMYOLYSIS AND NUMBERS OF PRESCRIPTIONS FOR ALL STATINS DISPENSED IN THE UNITED STATES SINCE THESE PRODUCTS WERE LAUNCHED.

VARIABLE	LOVASTATIN	PRAVASTATIN	SIMVASTATIN	FLUVASTATIN	ATORVASTATIN	CERIVASTATIN	TOTAL
Date approved	8/31/87	10/31/91	12/23/91	12/31/93	12/17/96	6/26/97	—
Fatal cases of rhabdomyolysis*	19	3	14	0	6	31	73
No. of prescriptions dispensed since marketing began†	99,197,000	81,364,000	116,145,000	37,392,000	140,360,000	9,815,000	484,273,000
Reporting rate (per 1 million prescriptions)‡	0.19	0.04	0.12	0	0.04	3.16	0.15

*U.S. cases reported to the FDA before June 26, 2001, that met the following criteria were included: the report included a clinical diagnosis of rhabdomyolysis, a temporal association between rhabdomyolysis and the use of a statin could be identified from the report, and death resulted either directly or indirectly from rhabdomyolysis.

†Data are through May 2001 and are from the National Prescription Audit Plus, excluding the Long Term Care Channel.

‡The reporting rate is the number of fatal cases divided by the number of prescriptions dispensed and is a crude measure of the number of reports received by the FDA relative to the extent of the use of an agent in the U.S. population. Rigorous comparisons between drugs that are based on these data are not recommended, since many factors can affect reporting and an unknown number of cases may not be attributed to the drug or reported to the FDA. Reporting rates are not incidence rates.

or statins. Myopathy and the rarer severe rhabdomyolysis are considered adverse events of therapy with this class of drugs.[1] Concomitant use of drugs that can increase blood levels of statins can increase the risk of myopathy, as can concomitant use of gemfibrozil.[2] We summarize the U.S. reports of fatal rhabdomyolysis associated with all six drugs in this class: lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin.

We reviewed reports in the Adverse Event Reporting System of the Food and Drug Administration (FDA). We also examined the number of prescriptions dispensed in the United States since the marketing of each drug began, according to the National Prescription Audit Plus (IMS HEALTH, Fairfield, Conn.). This is a nationally projected audit of retail pharmacies and mail-order houses.

Our results show that fatal rhabdomyolysis is a rare event among statin users, with reporting rates much lower than 1 death per million prescriptions in the case of most statins (Table 1). The rate of fatal rhabdomyolysis associated with cerivastatin therapy, however, is 16 to 80 times as high as the rates for any other statin. Some of this difference appears to be related to the known, marked interaction (relative to that of other statins) between cerivastatin and gemfibrozil, which in late 1999 led to the listing on the labels of contraindications against the combined use of these agents. The use of this combination was reported in 12 of the 31 deaths. After the exclusion of the 12 cases in which gemfibrozil was used with cerivastatin and the 7 cases in which it was used with lovastatin, the reporting rate of fatal rhabdomyolysis in association with cerivastatin monotherapy is 1.9 per million prescriptions, 10 to 50 times as high as the rates associated with the other statins. Among the 19 deaths associated with cerivastatin in the absence of gemfibrozil therapy, 12 occurred after use of the 0.8-mg dose (which was approved in the United States in July 2000), 6 occurred after use of the 0.4-mg dose, and the dose was not reported in 1 case. This pattern suggests that there is a relation to the dose.

Because of the underreporting of adverse reactions, the use of reporting rates as proxy measures of risk has limitations. Only about 1 percent of all serious events are directly reported by physicians.[3] There is a secular trend of increased reporting to the FDA over the past decade.[4] However, the rate of reports of fatal rhabdomyolysis associated with the use of atorvastatin (approved for use within six months after the approval of cerivastatin) was far less than for cerivastatin. Thus, the increased reporting associated with the use of cerivastatin appears to be more than an artifact related to an increased awareness of statin-associated rhabdomyolysis or to secular trends in reporting.

On the basis of the finding of a markedly increased reporting rate of fatal rhabdomyolysis in association with cerivastatin, Bayer, with the concurrence of the FDA, moved to withdraw cerivastatin from the U.S. market. Clinicians should be aware of this labeled but rare event associated with the use of all statins and should warn patients to watch for symptoms of myopathy, such as muscle pain or weakness, which should prompt an immediate consultation with their physician.

(The views expressed are those of the authors and do not necessarily represent those of, nor imply endorsement by, the FDA or the U.S. government.)

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