

Severe Liver Injury after Treatment with the Leukotriene Receptor Antagonist Zafirlukast

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Background: In registration trials, zafirlukast, an asthma medication, caused asymptomatic elevated aminotransferase levels in up to 5% of participants. Until now, however, no cases of severe hepatitis attributed to zafirlukast have been reported.

Objective: To report the clinical characteristics of three patients with severe hepatitis due to zafirlukast.

Design: Case report.

Setting: One community hospital and two university hospitals.

Patients: Three middle-aged women taking zafirlukast, 20 mg twice per day.

Intervention: Discontinuation of zafirlukast therapy in three patients, steroid therapy in two patients, and orthotopic liver transplantation in one patient.

Measurements: Serum aminotransferase and bilirubin levels,

standard blood tests for causes of hepatitis other than drug toxicity, and liver biopsy in two patients.

Results: Patient 1 recovered spontaneously, had a severe relapse after inadvertent rechallenge with the medication, and ultimately made a complete recovery. Patient 2 developed subfulminant hepatic failure and required liver transplantation. Patient 3 developed severe hepatitis that improved after treatment with corticosteroids. Liver tissue was available from two patients and showed histologic changes commonly associated with drug reactions.

Conclusion: Patients receiving zafirlukast may develop severe liver injury and should be observed for signs and symptoms of hepatitis.

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Cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄) are endogenously produced arachidonic acid metabolites that play an important role in the development of pulmonary inflammation and bronchoconstriction in persons with reactive airway disease. Members of a new class of drugs, leukotriene receptor antagonists, decrease airway edema and smooth-muscle constriction in persons with asthma (1–3). Zafirlukast (Accolate, Zeneca Pharmaceuticals, Wilmington, Delaware) is currently the most widely prescribed leukotriene receptor antagonist approved for the treatment of asthma.

Few toxic side effects have been reported in patients treated with zafirlukast or other leukotriene receptor antagonists. Asymptomatic increases in serum liver enzyme levels of two to three times the upper limit of normal were seen in 1.5% of 4058 patients taking zafirlukast during premarketing trials; no severe hepatotoxicity was noted (4). We describe three patients who developed severe hepatitis while taking zafirlukast.

PATIENT 1

A 42-year-old woman was referred for evaluation of hepatitis. The patient had a 10-year history of chronic sinusitis and asthma requiring intermittent prednisone

therapy. Eighteen months before presentation, treatment was begun with zafirlukast, 20 mg twice per day. Results of baseline liver tests were normal. Nine months after the patient began taking zafirlukast, however, serum aspartate aminotransferase and alanine aminotransferase levels were 2.63 μ kat/L and 4933 nkat/L, respectively. The patient was asymptomatic, but therapy was discontinued and a different leukotriene receptor antagonist, montelukast, was prescribed instead. Follow-up serum aminotransferase levels were normal 4 months later, and treatment with zafirlukast was resumed in place of montelukast. Two months later, the patient developed flu-like symptoms and jaundice and stopped taking zafirlukast. After 1 month of worsening symptoms, she sought medical attention. Her other medications were salmeterol xinafoate inhalation aerosol (Serevent, Glaxo Wellcome, Inc., Research Triangle Park, North Carolina), fluticasone propionate inhalation aerosol (Flovent, Glaxo Wellcome, Inc.), and fluticasone propionate nasal spray (Flonase, Glaxo Wellcome, Inc.). She did not drink alcohol, had no other known exposure to hepatotoxins, and had no risk factors for exposure to parenterally transmitted viruses. There was no family history of liver disease. On physical examination,

Table. Results of Laboratory Tests for Liver Injury and Causes of Hepatitis Other Than Zafirlukast Toxicity

Test	Result		
	Patient 1	Patient 2	Patient 3
Anti-hepatitis A virus IgG	Negative	Negative	Negative
Hepatitis B surface antigen	Negative	Negative	Negative
Hepatitis B surface antibody	Positive	Negative	Negative
Hepatitis B core antibody	Positive	Negative	Negative
Anti-hepatitis C virus antibody	Negative	Negative	Negative
Ferritin level	Normal	Normal	Not determined
Antinuclear antibody	Negative	Negative	Negative
Anti-smooth-muscle antibody	Negative	Negative	Not determined
Ceruloplasmin level, mg/L	Not determined	>200	>200
Peak level			
Alanine aminotransferase, nkat/L	4933	15 134	20 184
Bilirubin, $\mu\text{mol/L}$ (mg/dL)	12 (0.7)	669 (39.1)	347 (20.3)
Recovery level			
Alanine aminotransferase	Normal	Normal	Normal
Bilirubin	Normal	Normal	Normal
Peak level (rechallenge)			
Alanine aminotransferase, nkat/L	26 101	—	—
Bilirubin, $\mu\text{mol/L}$ (mg/dL)	106 (6.2)	—	—
Recovery level (rechallenge)			
Alanine aminotransferase	Normal	—	—
Bilirubin	Normal	—	—

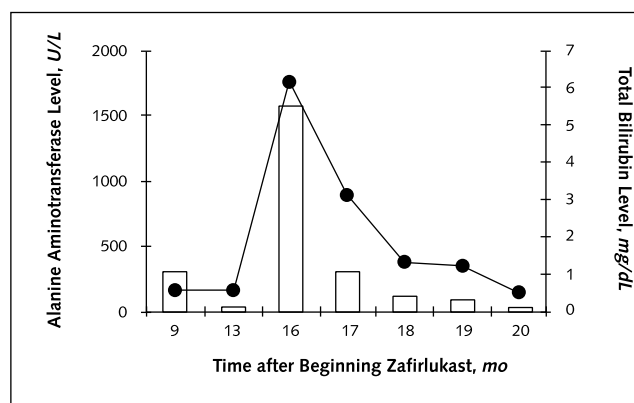
she was icteric but had no cutaneous stigmata of chronic liver disease. Her abdomen was not tender, and she had no hepatosplenomegaly or ascites. Serum aspartate aminotransferase and alanine aminotransferase levels were markedly abnormal; laboratory evaluation did not reveal evidence of viral, metabolic, or autoimmune liver disease (Table, Figure). Her symptoms gradually resolved, and after stopping zafirlukast treatment a second time, her serum enzyme levels returned to normal over a 6-month period.

PATIENT 2

A 49-year-old woman with chronic asthma presented with vomiting, fatigue, and a pruritic rash. She had been taking zafirlukast, 20 mg twice per day, for approximately 5 months, in addition to theophylline and albuterol sulfate tablets (Volmax, Muro Pharmaceutical, Inc., Tewksbury, Massachusetts) and ipratropium bromide (Atrovent, Boehringer Ingelheim, Ridgefield, Connecticut), albuterol sulfate (Proventil, Schering Corp., Kenilworth, New Jersey), and fluticasone propionate inhalation aerosols. Serum alanine aminotransferase and bilirubin levels, which had previously been normal, were 19 267 nkat/L and 41 $\mu\text{mol/L}$ (2.4 mg/dL), respectively. She did not drink alcohol, had no risk factors for parenteral exposure to hepatitis viruses, and had

no family history of liver disease. Laboratory evaluation did not reveal any evidence of viral, metabolic, or autoimmune hepatitis (Table). Two weeks later, the patient was admitted to the hospital with worsening symptoms, and zafirlukast therapy was discontinued. On physical examination, she was icteric, without cutaneous stigmata of chronic liver disease, hepatosplenomegaly, or ascites. She had an erythematous, papular rash on her

Figure. Serum alanine aminotransferase (bars) and total bilirubin (solid line) levels in patient 1.



Zafirlukast therapy was withdrawn at month 9, restarted at month 13, and withdrawn permanently at month 16. To convert U/L to nkat/L, multiply by 16.667. To convert mg/dL to $\mu\text{mol/L}$, multiply by 17.104.

chest, forehead, and back. Results of liver tests were abnormal (Table). There was no evidence of biliary obstruction. During the next 2 weeks, her clinical condition did not change, and she was discharged for follow-up as an outpatient.

Two weeks later, the patient was readmitted to the hospital with fluid retention and confusion. Physical examination was remarkable for jaundice, ascites, and asterixis. The patient had a protracted hospital course with intermittent fevers; a persistent, diffuse, pruritic rash; and peripheral eosinophilia (percentage of eosinophils was as high as 30%). A skin biopsy was compatible with drug-induced or idiopathic erythema multiforme. A transjugular liver biopsy demonstrated submassive hepatic necrosis with abundant eosinophils. The patient was treated with oral prednisone, 60 mg/d, for 1 week without substantial improvement and ultimately underwent orthotopic liver transplantation 84 days after presentation. The explanted liver was firm and shrunken, weighing 1000 g. Histologic examination showed submassive to massive necrosis with regeneration but no histologic evidence of chronic liver disease. The patient's postoperative course was unremarkable, and she now has normal liver function.

PATIENT 3

A 43-year-old woman was admitted to the hospital with jaundice. She had been treated with zafirlukast, 20 mg twice per day, for 6 months. Her only other medication was albuterol sulfate delivered by metered-dose inhaler. Nineteen days before seeking medical attention, she lost her appetite, developed abdominal pain and jaundice, and stopped taking zafirlukast. She did not drink alcohol and had no risk factors for parenteral exposure to hepatitis viruses. On physical examination, she was icteric but had no hepatosplenomegaly or ascites. Laboratory evaluation did not reveal any evidence of viral, metabolic, or autoimmune liver disease (Table). Results of liver tests were abnormal and failed to improve during the next 3 weeks. A liver biopsy was performed, and the specimen revealed submassive hepatic necrosis. Treatment with intravenous methylprednisolone, 200 mg every 4 hours, for presumed drug-induced liver injury was begun; symptoms and liver test results improved rapidly (Table).

DISCUSSION

By blocking the CysLT₁ leukotriene receptor, zafirlukast inhibits migration of inflammatory cells into the lungs after an allergenic challenge, decreasing airway edema and smooth-muscle constriction in patients with asthma (1–3). Because of its efficacy, convenient oral dosing, and apparent safety, zafirlukast has been recommended as first-line therapy for patients with mild, persistent asthma (3). To date, more than 1 million persons have been treated with zafirlukast, making it one of the 200 most-prescribed drugs in the United States (5).

Abnormal serum aminotransferase levels have been noted in some patients treated with high doses of zafirlukast (80 mg twice daily); the current dosage approved by the U.S. Food and Drug Administration is 20 mg twice daily (4, 6). In one clinical trial in which participants received 20 mg of zafirlukast twice daily, serum aminotransferase levels more than twice the upper limit of normal were seen in 3.1% of those in the zafirlukast group and 2.8% of those in the placebo group, a difference that was not statistically significant (7). Abnormal liver test results were asymptomatic and eventually returned to normal, usually within the first 3 months of continued treatment or after discontinuation of therapy with the drug (7). Cases of hepatitis with hyperbilirubinemia have been reported to the manufacturer with the use of the recommended dose (4). To the best of our knowledge, however, clinically significant hepatotoxicity related to this increasingly popular medication has not been reported up to now.

Evidence that zafirlukast was the cause of hepatic injury in our three patients is fourfold. First, other potential causes of acute hepatitis, including viral, autoimmune, and metabolic liver diseases, were excluded in each patient. Second, in the two patients who had liver biopsies, histologic characteristics were consistent with toxic injury. Third, one of the three patients had signs of systemic hypersensitivity (rash, fever, and eosinophilia), suggesting a drug reaction. Finally, and most important, in patient 1, rechallenge with zafirlukast resulted in recurrent hepatitis. This type of rechallenge phenomenon is considered diagnostic of drug-induced liver injury (8), although it may be dangerous and should seldom, if ever, be done intentionally.

The means by which zafirlukast causes liver injury are unknown. The idiosyncratic nature of its hepatotox-

icity, the evidence of hypersensitivity in patient 2, and the presence of hepatic eosinophils in all three patients suggest an immunologic mechanism. The apparent response to steroids in patient 3 also may support an immunoallergic cause (8). Possibly the most common severe adverse effect reported to date in patients treated with zafirlukast is the Churg–Strauss syndrome, a granulomatous, necrotizing, eosinophilic vasculitis that is itself of immunologic origin (9). Alternatively, the cytochrome P450 (CYP2C9 isoenzyme) pathway responsible for methylhydroxylation of zafirlukast during its metabolism may create one or more hepatotoxic intermediates that caused the liver damage in our patients (6). Of interest, all of our patients were women, and evidence suggests that cytochrome P450 is more active in women than in men (10).

Whatever its mechanism, hepatotoxicity related to zafirlukast is clearly idiosyncratic and occurs in a small minority of patients. The Acute Liver Failure Study Group, a consortium of 20 academic medical centers cooperating in the prospective collection of data concerning the cause of disease, treatment, and outcome of patients with acute liver failure (11) has to date not identified any other cases of severe liver injury attributable to zafirlukast (Lee WM. Personal communication). As a result, it is not possible to predict which patients treated with this drug will develop hepatitis. The section describing zafirlukast in the most recent edition of *Physicians' Desk Reference* has been revised to indicate that severe hepatitis and even liver failure may occur in patients receiving this medication (12).

Several potentially important clinical features of these three cases should be noted. First, in contrast to the clinical trials, in which some participants developed asymptomatic aminotransferase elevations during the first 3 months of therapy (6), hepatitis occurred in our patients only after several months of zafirlukast treatment. Second, in each of our patients, liver injury persisted for many weeks after zafirlukast was withdrawn; indeed, in patient 2, progressive hepatitis required liver transplantation nearly 3 months after zafirlukast therapy was discontinued. It is not known whether recognition of liver injury at an earlier stage (for example, through surveillance) may have prevented substantial morbidity. Finally, patient 3 seemed to have rapid clinical improvement after treatment with high-dose corticosteroids. There are, however, conflicting reports in the medical

literature regarding use of corticosteroids in the treatment of drug-induced hepatitis, and patient 2 did not have a convincing therapeutic response to steroid therapy (8). Therefore, the role of steroids in the treatment of zafirlukast-associated liver injury, like the role of surveillance liver tests, is currently undefined and should probably be considered on a case-by-case basis.

In summary, the three cases presented here illustrate that patients receiving the novel asthma drug zafirlukast can develop severe, symptomatic, acute hepatocellular injury, and even subfulminant hepatic failure. Physicians should be aware that zafirlukast is a potentially hepatotoxic drug, and patients treated with this medication should be observed for signs and symptoms of hepatitis.

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References

1. Wenzel SE. New approaches to anti-inflammatory therapy for asthma. *Am J Med.* 1998;104:287-300. [PMID: 0009552092]
2. Garcia-Marcos L, Schuster A. New perspectives for asthma treatment: anti-leukotriene drugs. *Pediatr Allergy Immunol.* 1999;10:77-88. [PMID: 0010478608]
3. Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med.* 1999;340:197-206. [PMID: 0009895400]
4. Accolate (zafirlukast) tablets [package insert]. Wilmington, DE: Zeneca Pharmaceuticals; 1997.
5. *American Druggist.* 1999;Feb:42-3.
6. Calhoun WJ. Summary of clinical trials with zafirlukast. *Am J Respir Crit Care Med.* 1998;157:S238-46. [PMID: 0009620946]
7. Fish JE, Kemp JP, Lockey RF, Glass M, Hanby LA, Bonuccelli CM. Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. The Zafirlukast Trialists Group. *Clin Ther.* 1997;19:675-90. [PMID: 0009377612]
8. Farrell GC. Liver disease caused by drugs, anesthetics, and toxins. In: Sleisenger & Fordtran's *Gastrointestinal and Liver Disease*. 6th ed. Feldman M, Sleisenger MH, Scharschmidt BF, eds. Philadelphia: WB Saunders; 1998:1221-52.
9. Wechsler ME, Pauwels R, Drazen JM. Leukotriene modifiers and Churg-Strauss syndrome: adverse effect or response to corticosteroid withdrawal? *Drug Saf.* 1999;21:241-51. [PMID: 0010514017]
10. Watkins PB, Murray SA, Winkelman LG, Heuman DM, Wrighton SA, Guzelian PS. Erythromycin breath test as an assay of glucocorticoid-inducible liver cytochromes P-450. Studies in rats and patients. *J Clin Invest.* 1989;83:688-97. [PMID: 0002913056]
11. Fontana RJ, McCashland TM, Benner KG, Appelman HD, Gunartanam NT, Wisecarver JL, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. The Acute Liver Failure Study Group. *Liver Transpl Surg.* 1999;5:480-4. [PMID: 0010545534]
12. Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2000:535-6.

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Inman had taken his own during the fighting outside Petersburg. When his two nearest companions pulled away his clothes and looked at his neck, they had said him a solemn farewell in expectation of his death. We'll meet again in a better world, they said. But he lived as far as the field hospital, and there the doctors had taken a similar attitude. He was classed among the dying and put aside on a cot to do so. But he failed at it. After two days, space being short, they had sent him on to a regular hospital in his own state. All through the mess of the field hospital and the long grim train ride south in a box car filled with wounded, he had agreed with his friends and the doctors. He thought he would die. About all he could remember of the trip was the heat and the odors of blood and of shit, for many of the wounded had the flux. Those with strength to do so had knocked holes in the sides of the wood boxcars with the butts of rifles and rode with their heads thrust out like crated poultry to catch the breeze.

Charles Frazier
Cold Mountain
New York: Atlantic Monthly Press; 1997:3-4

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