letters

Probable montelukast-induced hepatotoxicity in a pediatric patient: case report

To the Editor: Drug-induced liver injury is a potential complication of many medications. Montelukast and zafirlukast are competitive and selective leukotriene-receptor antagonists (LTRA) approved for the prophylaxis and chronic treatment of asthma in pediatric patients and adults. These LTRA are usually well tolerated. Montelukast is extensively metabolized by the hepatic microsomal cytochrome P450 3A4 and 2C9.[1] Hepatotoxicity has been associated with not only zafirlukast, but recent reports have also described elevated liver enzyme levels, hepatitis, and fulminant hepatic failure induced by montelukast.[2-8] However, all the described cases are adult patients and there have been no similar reports with montelukast in children. We present a patient who we believe is the first pediatric case of acute hepatitis while receiving montelukast.

A 5-year-old boy was admitted to our hospital with fatigue, nausea, vomiting and abdominal pain. The patient had a history of chronic bronchial asthma. He had been prescribed montelukast at a 5 mg daily dose for the last 2 years. On physical examination, he was not icteric, the abdomen was nontender, and no hepatosplenomegaly or ascites were present. Examination of other systems were normal. At presentation, the aspartate aminotransferase (AST) level was 990 IU/L (normal, 15 to 55 IU/L), the alanine aminotransferase (ALT) level was 658 IU/L (normal, 5 to 45 IU/L), the glutamyltranspeptidase level was 145 IU/L (normal, 5 to 32 IU/L), the total bilirubin level was 2.8 mg/dL, the indirect 0.7 mg/dL, the direct 2.1 mg/dL, and the ALP level was 445 IU/L (normal, 45 to 420 IU/L). The hepatic synthetic function was intact as indicated by a normal serum albumin level and PT. An abdominal ultrasound showed normal hepatic morphology. Viral serologic tests were negative.

There was no history of using other drugs, no risk factors for exposure to parenterally transmitted viruses or other hepatotoxins, and no family history of liver disease. Montelukast was discontinued with the development of symptoms. AST, ALT, bilirubin, ALP, and glutamyltransferase levels normalized within two weeks. Montelukast-induced hepatitis was suggested by rapid improvement after dechallenge, the exclusion of other causes of hepatitis and by comparison with the reports of similar cases. A liver biopsy had not been done.

Using LTRA in the treatment and prophylaxis of allergic asthma in childhood is gradually becoming more prevalant. The side effects of montelukast have rarely been reported, except for sporadic cases of urticaria, angioedema, erythema nodosum, and Churge-Strauss syndrome in adults.[9,10] One patient presented with pemphigus after using montelukast.[11] Recently, several cases of hepatotoxicity with zafirlukast and rarely, montelukast, were reported, but none included pediatric patients.

The mechanism of hepatotoxicity associated with LTRA is not clearly defined. Not infrequently drug-induced hepatotoxicity appears after a latency period as long as 2 years,[7] but the reported cases related to montelukast and zafirlukast had latency periods between 5 to 24 months.[2,3,6,7] This pattern may be similar to phenprocoumon-induced hepatitis, which has a latency period of typically 6 months and more.[7] This phenomenon is still not fully described. Besides this, other mechanisms of hepeatotoxicity, like hepatotoxic metabolites, idiosyncrasy, drug reactions and immunologic mechanisms are hypothesized.[2,8] In liver biopsy, histological findings from previously published reports described mild chronic inflammation in portal areas , without lobular inflamation or fibrosis.[8]

Clinical trials of montelukast showed no significant difference in liver function abnormalities between the montelukast group and the placebo group (2.1% of 1955 montelukast recipients had an increased ALT level vs. 2.0% of 1180 placebo recipients, and 1.6% of montelukast recipients developed self-limited, transient increases in AST levels vs. 1.2% of placebo recipients).[12] To our knowledge, this is the first reported case of drug-induced hepatitis probably caused by montelukast in a child.

A review of all reported cases of leukotriene modifier-induced hepatitis revealed that hepatic toxicity may develop within weeks or as late as 24 months after initiating therapy.[7,8] With the increasing use of these drugs, which has coincided with monitoring of liver function, more asymptomatic cases may come on the scene. Because of their efficacy, convenient oral dosing and apparent safety, the LTRA, montelukast and zafirlukast, have become frequently prescribed drugs for the therapy of asthma. To date, serial liver function testing is not recommended for patients receiving zafirlukast or montelukast,[2,8,13] but physicians should be aware of a potential hepatotoxic effect of montelukast, which may occur after many months of drug initiation. Periodic screening of liver function tests seems like a more prudent approach.

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REFERENCES

1. Chiba M, Xu X, Nishime JA, Balani SK, Lin JH. Hepatic microsomal metabolism of montelukast, a potent leukotriene D4 receptor antagonist, in humans. Drug Metab Dispos 1997;25:1022-1031.
2. Reinus JF, Persky S, Burkiewicz JS, Quan D, Bass NM, Davern TJ. Severe liver injury after treatment with the leukotriene receptor antagonist zafirlukast. Ann Intern Med 2000;133:964-968.
3. Actis GC, Morgando A, Lagget M, David E, Rizzetto M. Zafirlukast-related hepatitis: report of a further case. J Hepatol. 2001;35:539-541.
4. Danese S, De Vitis I, Gasbarrini A. Severe liver injury associated with zafirlukast. Ann Intern Med 2001;135:930.
5. Moles JR, Primo J, Fernandez JM, Hinojosa JE. Acute hepatocellular injury associated with zafirlukast. J Hepatol 2001;35:541-542.
6. Sass DA, Chopra KB, Wu T. A case of montelukast-induced hepatotoxicity. Am J Gastroenterol 2003;98:704-705.
7. Russmann S, Iselin HU, Meier D, Zimmermann A, Simon HU, Caduff P, et al. Acute hepatitis associated with montelukast. J Hepatol 2003;38:694-695.
8. Goldstein MF, Anoia J, Black M. Montelukast-induced hepatitis. Ann Intern Med 2004;140:586-7.
9. Minciullo PL, Saija A, Bonanno D, Ferlazzo E, Gangemi S. Montelukast-induced generalized urticaria. Ann Pharmacother 2004;38:999-1001.
10. Guilpain P, Viallard JF, Lagarde P, Cohen P, Kambouchner M, Pellegrin JL, et al. Churg-Strauss syndrome in two patients receiving montelukast. Rheumatology 2002;41:535-539.
11. Cetkovska P, Pizinger K. Childhood pemphigus associated with montelukast administration. Clin Exp Dermatol 2003;28:328-329.
12. Singulair tablets and chewable tablets (montelukast sodium). Physicians' Desk Reference. Montvale, NJ: Medical Economics 2002:2181-2185.
13. Accolate tablets (zafirlukast). Physicians' Desk Reference. Montvale, NJ: Medical Economics 2002:657-659.