ACUTE LIVER INJURY IN A GLATOPA-TREATED PATIENT WITH MS

Hepatotoxicity is rarely associated with glatiramer acetate (GA) treatment of relapsing MS. Here, we report a case of acute liver injury associated with generic GA (Glatopa, manufactured by Sandoz, a Novartis company, Holzkirchen, Upper Bavaria, Germany).

Case report. A 36-year-old woman presented with unilateral optic neuritis from which she recovered. Optic neuritis recurred at age 42. Brain MRI showed unilateral optic neuritis from which she recovered.

PATIENT WITH MS ACUTE LIVER INJURY IN A GLATOPA-TREATED

A liver biopsy showed severe portal, interface and panacinar, lymphocyte-predominant inflammation, with confluent necrosis, numerous apoptotic hepatocytes, and central perivenulitis (figure, B and C). The bile ducts were intact, and there was no significant ductular reaction. Steatosis, cholestasis, and fibrosis were not present. The patient was treated with IV corticosteroids followed by a several month taper of prednisone for possible autoimmune hepatitis. The patient’s liver function tests normalized within 2 months.

Discussion. GA is a synthetic random copolymer of 4 amino acids (glutamic acid, lysine, alanine, and tyrosine) approved for treatment of relapsing-remitting MS. With more than 2,000,000 patient-years of exposure to GA, there are 13 published cases of hepatotoxicity (table e-1 at Neurology.org/nn). Previously reported cases are notable for prior treatment with interferon β, concomitant use of other potentially hepatotoxic drugs, and symptom onset 1–8 months after initiating GA. We report a rare case of acute liver injury in the setting of generic GA use. Liver injury associated with GA presents with a hepatocellular injury pattern without hyperglobulinemia, although autoimmune hepatitis can occur (Supplemental Table). Given our patient’s negative autoimmune markers, lack of plasma cells on biopsy, and resolution of liver injury on a rapid prednisone taper, it is unlikely that this patient had autoimmune hepatitis. The administration of influenza and meningococcal vaccines seems unlikely to be contributory because neither vaccine is hepatotoxic. Seven years prior to the diagnosis of MS, our patient had a history of transaminitis, which was attributed to a viral etiology (associated with serologic evidence of prior hepatitis A and hepatitis E virus exposure), followed by many years of normal liver enzymes.

GA is classified as a nonbiological complex drug (NBCM) whose composition and in vivo activity are highly dependent on manufacturing processes.1,2 Systemic toxicities are extremely rare with GA, and there are no guidelines for drug safety monitoring. In prior clinical trials of Copaxone and generic GA, the incidence of liver dysfunction was equivalent to that of placebo-treated patients.3 Since approval, over 300 cases of Copaxone-associated liver-related abnormalities were reported to the United States Food and Drug Administration (US-FDA). In animal studies, transaminase elevations were observed with chronic high-dose GA.
Significant hepatotoxicity, nephropathy, and skin reactions also occurred with protiramer (TV-5010), a glatiramoid with a higher molecular weight of the same molar ratio of amino acids as GA.\textsuperscript{4}

Glatopa was approved as a GA biosimilar compound in 2015 without a requirement for proof of either efficacy or safety in clinical trials. Sandoz demonstrated Glatopa’s equivalence with Copaxone by similarities in chemistry, polymerization, biological, and immunologic properties.\textsuperscript{5,6} In a study by the US-FDA using 3 different analytic measures, distinct physicochemical differences were found between Copaxone and commercially available copolymer-1.\textsuperscript{7} Teva Pharmaceuticals also found differences in charge distribution, molecular density, monomolecular size, and the existence of a novel polypeptide group in Glatopa compared with Copaxone.\textsuperscript{2} Therefore, differences in manufacturing between these NBCDs could cause different adverse event profiles. Given that generic GA is only recently available for clinical use in MS and is the likely cause of acute liver injury in the present case report, heightened awareness of possible liver dysfunction and other adverse effects may be warranted.

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Liver function tests (panel A) were performed from February 17, 2016 (32 days prior to glatiramer acetate [GA]) to June 13, 2016 (102 days following the start of GA treatment). The gray rectangle represents the 13 days of GA treatment starting at day 0. Alanine transaminase (ALT) (normal range 10–30 U/L) and aspartate aminotransferase (AST) (normal range 6–29 U/L) are depicted on the left y-axis and alkaline phosphatase (alk phos [normal range 33–115 U/L]) on the right y-axis. Liver biopsy (indicated by “Bx” on panel A) on day 20 shows dense portal lymphocytic inflammation (panel B) with interface activity and normal bile ducts and shows lobular lymphocytic inflammation with confluent necrosis (panel C) (hematoxylin and eosin stain, 200×). This histologic picture along with the clinical presentation and temporal profile is consistent with drug-induced liver injury.
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