LETTER TO THE EDITOR

Does glatiramer acetate provoke hepatitis in multiple sclerosis?

Abstract
An association between multiple sclerosis and autoimmune hepatitis has been described. The latter can also be unmasked or exacerbated by a variety of therapies used in multiple sclerosis, such as beta-interferon or glatiramer acetate.

Two cases of hepatitis occurring after exposure to glatiramer acetate are described here: the first, was possibly due to autoimmune hepatitis, rather than glatiramer acetate induced liver injury, the second was definite autoimmune hepatitis. Both occurred in patients who had already experienced hepatitis exacerbations during previous beta-interferon treatment.

We suggest that glatiramer acetate can unmask hepatitis. Thus, liver enzyme monitoring should be undertaken frequently in those patients with multiple sclerosis receiving glatiramer acetate, with a history of hepatitis during treatment with interferon beta-1a.

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1. To the editor

Dear Sir,

An association has been described between multiple sclerosis (MS) and autoimmune hepatitis (AIH) (Ferrò et al., 2008).

Immunomodulatory treatments for MS have also been associated with hepatitis flare-ups (HF). Previous reports, have been connected mainly with interferon beta-1a (Grieco et al., 2007; Duchini, 2002), but a few instances have been ascribed to glatiramer acetate (GA) (Neumann and Csepregi, 2007; von Kaickreuth et al., 2008). Here we describe two further cases of HF related to GA.

Case 1. A 41-year-old woman was diagnosed with relapsing-remitting MS in October 2008. Two weeks after initiation of IFN beta-1a she experienced an HF which spontaneously recovered after IFN withdrawal.

In October 2009, GA was started because of MS progression. One month later, she was admitted to a secondary referral center with acute hepatitis. Laboratory findings showed aspartate aminotransferase (AST) levels of 1612 IU/l (normal values: 13-41 IU/l) and alanine aminotransferase (ALT) levels of 4410 IU/l (normal values: 9-63 IU/l) respectively, slight elevation of bilirubin (5 mg/dL) and marked elevation of cholestatic liver enzymes (alkaline phosphatase 383 IU/l, Gammaglutamyl Transferase 236 IU/l); gamma globulin levels were 1.1 gr/dl and International Normalized Ratio (INR) was normal; viral markers for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), Epstein Barr Virus (EBV) were negative; Smooth Muscle Antibodies (SMA), Liver Kidney Microsome Antibodies (LKM), Anti Mitochondrial Antibodies (AMA), Antineutrophil cytoplasmic antibodies (ANCA) were negative, while Anti Nuclear Antibodies (ANA) Hep2 was positive 1:320 (homogeneous pattern). There was no family history of autoimmune disease. GA was discontinued and followed by rapid reduction of liver enzymes. When the patient was referred to our unit, one month later, AST and ALT were 82 UI/l and 173 UI/l respectively, whilst bilirubin and cholestatic liver enzymes were normal. Liver biopsy showed moderate interface hepatitis (a process of inflammation and erosion of the hepatic parenchyma at its junction with portal tracts), with eosinophilic infiltrate and porto-portal fibrosis (Fig. 2). The International Autoimmune Hepatitis Group (IAHG) score was 11, suggesting a diagnosis of probable AIH (according to this score, AIH is probable with a result between 10 and 15, and it is definite with a result of more than 15) (Alvarez et al., 1999).

However, the diagnosis of AIH remained uncertain because of the spontaneous and rapid reduction of liver enzymes, the absence of hypergammaglobulinemia and the strong correlation with drug exposure, which could resemble an HF...
explained solely by drug-induced liver injury. The patient was kept under review at our unit, and liver enzymes remained normal at the last visit, 18 months later.

Case 2. A 29-year old woman was diagnosed with relapsing remitting MS and treated with Interferon beta-1a in May 2008. This was followed (two weeks after the initiation of the treatment) by an increase of aminotransferases which promptly subsided after Interferon beta 1-a withdrawal but unfortunately the MS relapsed. In July 2009 GA was started as second-line treatment, but it was stopped one month later because of abrupt onset of jaundice, asthenia and marked hypotension. In August 2009 the patient was referred to our unit. On admission, laboratory findings showed AST levels of 820 IU/l, ALT levels of 1260 IU/l, alkaline phosphatase levels of 342 IU/l, gamma glutamyl transferase levels of 205 IU/l, bilirubin 4 mg/dl, INR 1.0. Viral markers for HCV, HBV, HIV, CMV and EBV were negative. ANA Hep2 were positive (1:160 with a homogeneous pattern), whilst SMA, LKM, AMA, ANCA were negative; gamma globulin level was 1.8 gr/dl. No family history of autoimmune disease was reported. Liver biopsy showed marked lymphoplasmacitic infiltrate with portal-portal fibrosis and slight ductal proliferation (Fig. 1). The International Autoimmune Hepatitis Group (IAHG) score was 16, strongly suggesting a diagnosis of AIH (Alvarez et al., 1999).

Prednisone was started with progressive reduction of liver enzymes. Long-term treatment with low-dose prednisolone and azathioprine was required to maintain the liver enzymes within the normal range, because of elevated ALT levels whenever the steroid was withdrawn.

2. Discussion

An association between MS and AIH is not fully established. Autoimmune liver diseases, not related to drug treatment, have been reported in patients with MS, including autoimmune hepatitis and primary biliary cirrhosis, although women in general are more likely to be affected by these diseases and a typical MS population is 70% female. Several factors associated with the etiology, immunology and treatment of MS could all predispose the MS patient to liver injury (Tremlett and Oger 2004).

Immunological processes in MS include elevations in numerous cytokines which have been associated independently with liver injury including IFN-gamma, IL-2 and TNF-alpha. MS patients are regular users of non-prescription medicines, herbal remedies and other complementary medicines. Polypharmacy, particulary with cytochrome P450 enzyme inducing or inhibiting agents, increases the risk of drug-induced hepatotoxicity.

There are several reported cases of liver disturbances ranging from autoimmune hepatitis to fulminant liver failure and death in MS patients treated with specific drugs, other than beta-interferons Tremlett and Oger (2004). Some of these drugs are independently associated with liver injury such as pemoline, dantrolene, tizanidine, nitrofurantoin, azathioprine, whilst others were not previously, or were rarely associated with liver injury such as potassium p-aminobenzoate, ranitidine, alkaloid contamination of herbal remedies (skullcap and pau d’arco) (Tremlett and Oger, 2004).

Furthermore, an association has been described between GA and AIH (Neumann and Csepregi, 2007; von Kalckreuth et al., 2008).

The mechanism by which GA exerts its effects is not fully elucidated. One proposal is that it can induce T helper type 2 cells that cross-react with myelin basic protein (Aharoni et al., 1997), thus inducing autoimmune disease in patients who are genetically predisposed. The two cases in our report describe two different profiles of hepatitis both occurring shortly after GA initiation. The first was probable AIH, although drug-induced liver injury could not be excluded, while the second strongly resembled AIH. Both occurred in patients who had already experienced hepatitis attacks during previous Interferon-beta 1a treatment, exactly as described in previous reports (Neumann and Csepregi, 2007;
von Kalckreuth et al., 2008). Of particular interest is the patient described by Neumann and coworkers (Neumann and Csepregi 2007). He previously experienced two episodes of severe necrotizing hepatitis related to Interferon-beta 1a that was histologically and serologically proven AIH with onset two months after the start of treatment. There was no increase of gamma-globulin, but he displayed a good response to steroid treatment (Neumann and Csepregi 2007). This case is similar to our Case 1, although our patient recovered spontaneously. Conversely the female patient reported by von Kalckreuth and coworkers (von Kalckreuth et al., 2008), who previously experienced severe Interferon-beta 1a induced necrotizing hepatitis, presented with histologically and serologically proven AIH developing two months after the start of the treatment, and with an optimal response to steroidal treatment (von Kalckreuth et al., 2008). This case is very similar to our Case 2.

In conclusion, we highlight the fact that hepatitis flares may be observed in relation to GA treatment. The mechanism may be either drug-induced liver injury or autoimmune hepatitis. Our data support what is reported in the literature, and suggest that liver enzyme monitoring should be undertaken in those patients with MS during GA treatment, where there is a history of HF during previous treatment with Interferon beta-1a. Furthermore, autoimmune disease, especially AIH, should be excluded, and caution is advisable before prescribing GA in patients with concomitant liver disease.

**Conflict of interests**

None declared for all authors.

**References**


