Liver injury associated with the β-interferons for MS

To the Editor: Hepatotoxicity has been associated with all forms of interferon beta.[1] Autoimmune hepatitis (AIH), another hepatic complication of IFN (beta)-1a treatment for MS, has been reported.[2] We present an unusual case.

A 52-year-old woman with a 10-year history of multiple sclerosis (MS) was initially treated with glatiramer acetate from 1997 to 1999. In January 2000, IFN beta-1a (Avonex) was started after relapsing symptoms occurred and new MRI lesions appeared. In December 2002, she developed painless jaundice, a cholecystectomy was performed, and her jaundice resolved. Avonex was continued. Hepatic function tests were normal in February 2003. IFN beta-1a (Rebif) was instituted in early May 2003 because of worsening gait and progressive MRI changes. The patient received 8.8 mcg SC (20% of target dose) every other day for only six doses until she noted increasing fatigue and jaundice. There was no history of acetaminophen, ethanol, or nefazodone use. Physical examination revealed marked jaundice. Laboratory tests showed increased hepatic enzymes and total bilirubin of 28.6 mg/dL (0.2 to 1.3 mg/dL). Hepatitis panel and thyroid function tests were normal.

ANA screen was positive in a 1:320 homogenous pattern. Anti-smooth antibodies were positive at 1:40 titer. A CT of the abdomen revealed no biliary obstruction. Prednisone 20 mg/day was administered. Over the next several months there was a dramatic decrease in jaundice and bilirubin levels, and by March 2004 the total bilirubin was 0.8 mg/dL.

Autoimmune complications have been reported in MS patients treated with interferon alpha and interferon beta after several months.[2–4] The etiology of this immunologic complication is unclear but may involve disruption of vital intracellular functions, induction of antibody cytotoxicity, or mitochondrial injury.[5]

A previous case of AIH has been reported after a cumulative dose of 215 mcg of IFN (beta)-1a, however this patient had taken nefazodone.[4] Another patient on IFN (beta)-1a developed AIH after 24 months.[2] The patient reported here had signs and symptoms of hepatic dysfunction after only 51 mcg of Rebif had been administered in just six doses. At the onset of treatment with IFN (beta)-1a, patients with MS should be informed about possible hepatic complications of their medication since our patient developed signs and symptoms 2 weeks before her first recommended blood test at 1 month.

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To the Editor: The article on liver injury with IFN beta in MS by Tremlett et al.[1] prompts four comments.

First, Tremlett ranks IFN potency by MIU based on product monographs. Each product is tested on different assay systems rendering such comparisons invalid. Direct comparative data indicate that IFN beta-1a is approximately ninefold more biopotent than IFN beta-1b.[6] A more accurate ranking by potency would be IFN beta-1a SC 44 mcg TIW, IFN beta-1b SC 8 MIU (or 250 mcg) on alternate days, IFN beta-1a SC 22 mcg TIW, and finally IFN beta-1a IM 30 mcg QW.

Second, the authors cite mortality in 10 to 15% with ALT >3 ULN and Tbili >1.6 ULN. However, the mortality associated with Hy's rule rather refers to patients with jaundice (generally Tbili >3) and ALT > 3 ULN.[7] Thus one, and possibly two (of 835 patients) had this combination while no cases were seen in 1,995 patients exposed to IFN beta-1a at various doses in clinical trials,[8] making the risk very low, though not absent.

Third, the rate of ALT increase in PRISMS is cited as 19.6% and 27.2% and the authors imply this is lower than their values due to "vague reporting style" in clinical trials. The comparison is not relevant because the values in PRISMS refer to ALT elevation considered as adverse events by the physician, not to patients with laboratory evidence of ALT elevation, as per Tremlett et al. Because ALT elevations are predominantly mild, they are often not considered as clinically relevant, nor reported as adverse events. Rates of laboratory detected ALT elevations higher than those found by Tremlett et al. have been reported, including the fact that most are mild and self-limited.[8] This suggests that the level of ascertainment in the Tremlett et al. series was less thorough, presumably due to the retrospective nature of the study, than in prospective, controlled clinical study data in which placebo comparative results are also provided.

Finally, with respect to the suggestion that acetaminophen might increase liver dysfunction in patients receiving IFN therapy, concomitant use of IFN and acetaminophen in over 700 patients was associated with reduced, not increased, risk of ALT elevation compared to patients receiving IFN alone.[8] The brief report by Tremlett Tremlett et al. otherwise confirms previous reports on the high prevalence, but relatively low impact, of liver dysfunction with IFN therapy in MS. The suggested guidance regarding testing of liver function forms part of IFN product package inserts worldwide. It is important to understand, however, as noted by Tremlett Tremlett et al., that such monitoring may not prevent the rare occurrence of severe symptomatic cases.[9]

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Reply from the Authors: Case reports detailing unexpected adverse consequences of medications such as autoimmune hepatitis associated with beta-interferon by Drs. Wallack and Callon are of clinical importance. Such events may not occur within the context of a clinical trial due to limited time, patient numbers, and patient selection or even in a limited postmarketing study such as ours[1] due to exposure time and numbers of treated cases. Only when very large numbers of MS patients are treated with the licensed beta-interferons will cases such as this be reported. Pooling of such cases is then vital to facilitate the identification of emerging patterns, such as a preponderance of females developing severe hepatic injury associated with beta-interferon treatment in MS.[8]

We encourage others to report such cases should they arise and also to complete an adverse drug reaction report to the relevant National Health Authority. Most of these forms are available online, including in the United States,[10] Canada,[11] and the United Kingdom.[12] We welcome the comments from Drs. Francis and Alteri (Serono; manufacturers of beta-interferon-1a [Rebif]) and Dr. Kaplowitz. Answering each point raised in order:

1. Comparing the relative potency of the beta-interferons (IFNBs) is quite a challenge. Several different options were considered before the current methodology was decided upon. Using the ranking suggested by Francis et al. does not change our results in that a dose-response effect is still observed.

2. Unfortunately, neither our post-marketing study[1] nor the pooled results from 1995 IFNB treated trial patients[8] will give a true indication of the risk of severe hepatotoxicity associated with the beta-interferons for MS. Even if the risk of serious hepatotoxicity is deemed as fairly high (i.e., 1/10,000 to 1/50,000),[13] at least 30,000 to 150,000 MS patients need to be exposed to IFNB and every single case of serious hepatotoxicity reported before the true risk will be known (the rule of 3s).[14] Again, we encourage the reporting of such cases to the relevant National Health Authorities. Since submission and acceptance of our post-marketing study,[1] another alert warning health care professionals of hepatic injury associated with IFNB was issued by Health Canada[15] in conjunction with the Pharmaceutical Manufacturers of IFNB.

3. The vague reporting style refers to this exact problem highlighted by Francis et al. It is unclear in the PRISMS clinical trial report[16] that the numbers of patients with elevated ALT were not all the patients who developed elevated ALT, rather only those who individual physicians flagged as having an adverse event. This is not a consistent, reproducible, or acceptable way to report

adverse drug reactions in clinical trials. Hence there is an apparent sharp increase in the proportion of IFNB-1a (SC 44 mcg three times weekly) patients developing elevated ALT over a 2-year period—from 27.2% reported in PRISMS[16] to 67% reported in a part re-analysis of PRISMS/part pooling with other IFNB-1a clinical trials.[8]

4. We hypothesized that concomitant medication, particularly acetaminophen (paracetamol), known to cause hepatotoxicity and frequently recommended to MS patients as prophylaxis against the flu-like symptoms associated with IFNB treatment, might increase the risk of hepatoxocity.[1] Francis et al.[8] were able to show that acetaminophen was not a risk factor in IFNB-treated patients developing an elevation in ALT (>ULN), although propionic acid derivatives (including ibuprofen) did increase the risk in both the placebo and IFNB groups.[8]

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