Liver injury associated with the β-interferons for MS

A comparison between the three products

Helen L. Tremlett, PhD; Eric M. Yoshida, MD, MHSc, FRCPC; and Joel Oger, MD, FRCPC

Abstract—A population-based retrospective chart review of the biochemical liver tests of 844 patients with multiple sclerosis prescribed a β-interferon (IFNβ) product in British Columbia, Canada was performed between 1995 and 2001. Overall, 36.9% (243/659) of patients developed new elevations of alanine aminotransferase. All the IFNβs caused elevated aminotransferase levels compared with pretreatment levels ($p < 0.005$) and were higher than reported in clinical trials. Their relative effect on aminotransferases can be approximated as IFNβ-1b(subcutaneous [SC]) = IFNβ-1a(SC) > IFNβ-1a(IM).

NEUROLOGY 2004;62:628–631

Interferon (IFN) -α, -β, and -γ have been associated with hepatotoxicity. Subcutaneous (SC) IFNβ-1a and IFNβ-1b but not IFNβ-1a(IM) showed significant increases in aminotransferases compared with placebo in the pivotal clinical trials.[1-3] We report a postmarketing study comparing all three commercially available IFNβs.

Methods. We report a retrospective review of patients with multiple sclerosis (MS) prescribed an IFNβ in British Columbia between July 1995 and June 2001 and followed for at least 6 months. The British Columbia population was 4,058,833 in 2000. IFNβ-1b (SC, 250 μg alternate days) was licensed July 1995; IFNβ-1a (SC, 22 or 44 μg thrice weekly) was licensed February 1998; and IFNβ-1a (IM, 30 μg once weekly) was licensed April 1998. Reimbursement of an IFNβ required a prescription from one of the four MS clinics, patients aged 18 to 60 years with ≥2 relapses in the previous 2 years, and an Expanded Disability Status Scale (EDSS) ≤6.5. Drug costs prohibit most patients from gaining a private prescription outside of the MS clinics. No uniform protocol for liver tests existed during the study period; however, as a minimum, alanine and aspartate aminotransferases (ALT, AST), total bilirubin (Tbili), alkaline phosphatase (AP) and, until 1999, γ-glutamyltranspeptidase (GGT) were measured before treatment and months 3, 6, 12, and yearly thereafter. Stopping drug because of elevated results was at the physicians' discretion. Patients were free to visit any hospital or community laboratory. For analysis, liver tests were grouped into baseline (up to 6 months pretreatment), months >0 to 6, months >6 to 12, and yearly thereafter. When multiple tests were recorded, the highest value was used. Exclusion criteria included previous use of IFNβ or glatiramer acetate and comorbidity causing pretreatment elevated liver tests. Liver test results were recorded as a fraction of the upper limit of normal (ULN) provided by each laboratory. Aminotransferases were graded according to the World Health Organization criteria: grade 0 (≤ULN); grade 1 (>ULN to 2.5 ULN); grade 2 (>2.5 to 5 ULN); grade 3 (>5 to 20 ULN); and grade 4 (>20 ULN).

Statistical analyses were carried out using SPSS (version 10.0, Chicago, IL). A chi-square test compared categorical variables. Kruskall–Wallis test was used for interval results (non-normal), and McNemar test was used for "before-and-after" results. Student's t-test and repeated-measures analysis of variance were used for parametric variables and liver tests over time.

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Results. Eight hundred forty-six eligible patients were identified; 844 charts were available for review; and 835 patients had at least one liver test result recorded. There were significant pretreatment differences between the IFNβ groups (table 1). Mean time on drug for IFNβ-1b(SC) was 29.5 months, IFNβ-1a(SC) 15.7 months, and IFNβ-1a(IM) 14.7 months. The study covered 1,626 treated patient-years.

ALT results are presented in table 2, and AST results are available online (see table E-1 on the *Neurology* Web site; go to www.neurology.org). There were de novo grade 1, 2, and 3 elevations of ALT and AST in patients treated with IFNβ ($p < 0.05$). IFNβ-1a(SC) ($p < 0.005$) and IFNβ-1b(SC) ($p < 0.0005$), but not IFNβ-1a(IM) ($p > 0.05$), showed grade 2 de novo elevations in aminotransferases. The pattern of elevation differed, peaking within the first 6 months for IFNβ-1b(SC) and IFNβ-1a(SC) and later, between months 6 and 12, for IFNβ-1a(IM) (figure).

Direct dose comparisons of the IFNβs are difficult. Using the World Health Organization reference standards—available from the product information for IFNβ-1a(IM) and IFNβ-1b(SC)—and assuming equal activity between IFNβ-1a preparations, weekly doses approximate as 28 MIU for IFNβ-1b(SC), 26.4 MIU for high-dose IFNβ-1a(SC), 13.2 MIU for low-dose IFNβ-1a(SC), and 6 MIU for

From the University of British Columbia (Drs. Tremlett, Yoshida, and Oger); and Divisions of Neurology (Dr. Tremlett) and Gastroenterology (Dr. Yoshida), Department of Medicine, Vancouver Hospital & Health Sciences Centre, Vancouver, BC, Canada.

Dr. Helen Tremlett is supported by a Fellowship from the MS Society of Canada. The Special Therapy Program of the University of British Columbia MS Clinic is supported by Berlex Canada, Biogen, Serono, and Teva Neurosciences. Dr. Oger and the MS Clinic have received financial support from Berlex, Schering AG, Biogen, and Serono. He has served as a consultant and received honoraria and travel grants from Berlex, Biogen, Serono, and Teva-neurosciences.

Received April 14, 2003. Accepted in final form September 26, 2003.

Address correspondence and reprint requests to Dr. Helen L. Tremlett, Department of Medicine, Division of Neurology, Vancouver Hospital & Health Sciences Center, UBC Site, S159-2211 Wesbrook Mall, Vancouver, BC, V6T 2B5 Canada; e-mail: tremlett@interchange.ubc.ca

Table 1 *Baseline (pre-treatment) demographics*

	All IFNβ n = 844	IFNβ-1b (SC) n = 460	IFNβ-1a (SC) n = 322	IFNβ-1a (IM) n = 62	Statistical comparisons between IFNβs (3 groups)
Female	633 (75%)	341 (74%)	242 (75%)	50 (81%)	$p = 0.537$*
Age, y (at initiation of treatment) mean (SEM)	44.3 (0.32)	45.6 (0.42)	43.0 (0.54)	41.3 (1.18)	$p < 0.0005$†
Age, y (at onset of MS) Mean (SEM)	31.3 (0.34)	31.4 (0.45)	31.2 (0.54)	31.3 (1.38)	$p = 0.974$†
Disease duration y mean (SEM)	13.1 (0.30)	14.3 (0.40)	11.8 (0.47)	10.3 (1.13)	$p = 0.0005$†
EDSS§ Median	3.0	3.5	3.0	2.3	$p = 0.004$‡
Ethnicity					$p = 0.672$*
Caucasian	696(94.8%)	385(94.6%)	259(95.6%)	52 (93.0%)	
Noncaucasian	38 (5.2%)	22 (5.4%)	12 (4.4%)	4 (7.0%)	

Where group differences were found, a pair-wise post-hoc analysis was carried out using a Bonferroni correction. IFNβ groups that were not significantly different are represented by underlining.

* Pearson's χ^2.
† ANOVA.
‡ Kruskall-Wallis.
§ Within 1 year of starting IFNβ.

IFNβ = β-interferon; SC = subcutaneous; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale.

IFNβ-1a(IM). There was a dose-response effect within the first 6 months and during the entire study for de novo elevated (≥grade 1) ALT and AST (independent t-test, $p < 0.05$). For ALT elevations during the first 6 months, in order of decreasing equivalent doses, proportion of patients affected were 96 of 322 (29.8%), 37 of 124 (29.8%), 32 of 119 (26.9%), and 7 of 52 (13.5%; $p = 0.024$). There were marginal differences between the high- and low-dose IFNβ-1a(SC) groups, which were not significant for ALT elevations ($p > 0.05$). Injection frequency was associated with de novo elevated (≥grade one) ALT ($p = 0.005$) and AST ($p = 0.001$) during the first 6 months and the entire study period ($p = 0.018$ and $p = 0.004$).

When gender, disease duration, age at onset and at treatment initiation, and baseline EDSS were investigated as covariates, only gender was a predictor of de novo elevated aminotransferases ($p = 0.03$). Men were more likely than women to have elevated aminotransferases at baseline (11.5 vs 6.0%; $\chi^2 = 6.10$; df = 1; $p = 0.013$) and during treatment (60.6 vs 39.5%; $\chi^2 = 6.20$; df = 1; $p = 0.013$).

Elevated aminotransferases (>3 ULN) and Tbili >1.6 ULN are associated with 10 to 15% mortality.[4] This combination was measured in two patients within one[5] and 27 months of starting an IFNβ. The latter patient recovered subsequently when drug was stopped. Both patients developed jaundice. No other liver-related symptoms were re-

Table 2 *ALT elevations split according to IFNβ*

IFNβ	Pre-treatment (≥grade 1)	De novo during treatment (≥grade 1)	De novo during treatment (≥grade 2)	De novo during treatment (≥grade 3)
IFNβ-1b (SC)	23/382 (6.0%)	136/350 (38.9%)*	15/350 (4.3%)*	4/350 (1.1%)
IFNβ-1a (22 μg; SC)	11/146 (7.5%)	43/128 (33.6%)*	6/128 (4.7%)‡	2/128 (1.6%)
IFNβ-1a (44 μg; SC)	10/141 (7.1%)	49/129 (38.0%)*	10/129 (7.8%)†	2/129 (1.6%)
IFNβ-1a (SC)§	21/287 (7.3%)	95/257 (37.0%)*	17/257 (6.6%)*	5/257 (1.9%)
IFNβ-1a (IM)	1/55 (1.8%)	12/52 (23.0%)*	1/52 (1.9%)	0/52
All IFNβs	45/724 (5.3%)	243/659 (36.9%)*	33/659 (5.0%)*	9/659 (1.4%)†

A two-sided McNemar test was used to compare results to baseline (pre-treatment).

* ($p < 0.0005$).
† ($p < 0.005$).
‡ ($p < 0.05$).
§ 22 and 44 μg groups combined. The combined group includes the full history of patients who may have switched (without interruption) between low and high dose IFNβ-1a(SC) and vice versa; therefore, in some instances simple addition of the 22 μg and 44 μg groups does not equal the combined figures.

IFNβ = β-interferon; SC = subcutaneous.

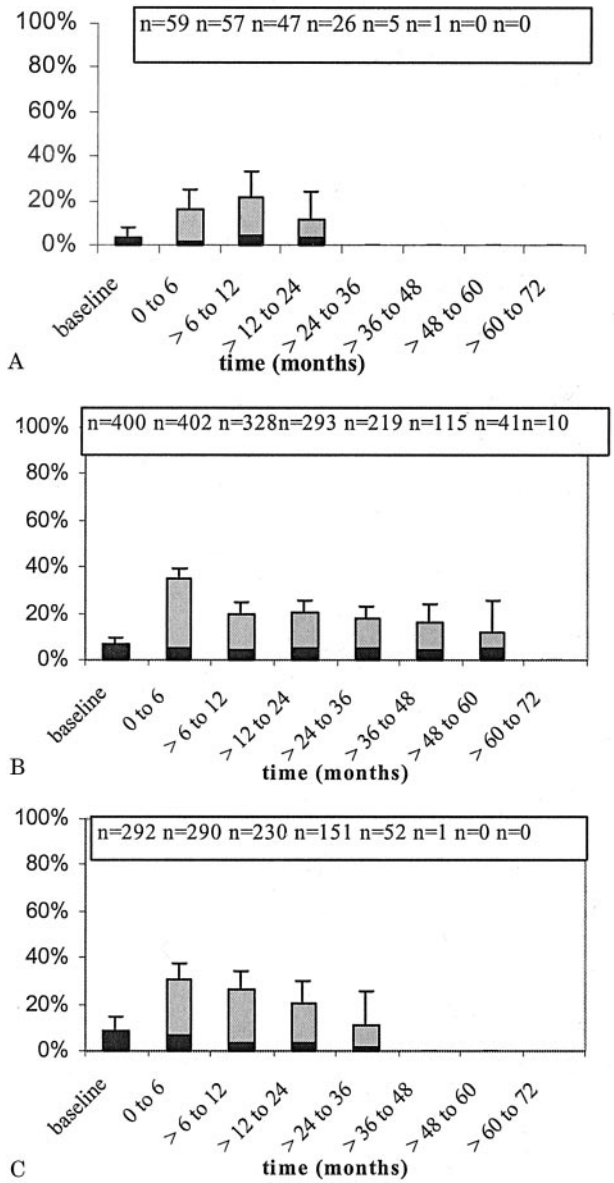

Figure. The percentage of interferon (IFN) β-treated patients with elevated aminotransferases over time (≥grade 1). (A) IFNβ-1a(IM). (B) IFNβ-1b(SC). (C) IFNβ-1a(SC). If ≤10 patients are given a drug, data are not depicted on bar chart. Error bars represent 95% CI for a proportion. The follow-up period differed between the IFNβ groups. Mean time on drug for IFNβ-1b(SC) was 29.5 months, IFNβ-1a(SC) 15.7 months, and IFNβ-1a(IM) 14.7 months. ▨ *= Patients with de novo elevated alanine and aspartate aminotransferases (ALT/AST);* ■ *= patients with elevated ALT/AST from baseline.*

ported. Of the 239 of 284 (84%) patients who continued IFNβ treatment despite aminotransferase elevations, 167 of 216 (77%) reached grade 1 toxicity and then returned to within normal limits compared with 14 of 22 (64%) reaching grade 2 and 1 patient reaching grade 3. Of the patients (55/748; 7.4%) with high baseline aminotransferases, 16 of 53 (30%) experienced at least a further one-grade elevation, although 23 of 53 (43%) returned to within normal levels at the study close (2 patients had no further results). The AST-to-ALT ratio was >2 in 9 of 289 (3%) patients with de novo elevated aminotransferases. De novo elevations in Tbili affected 28 of 690 (4.1%) patients, in AP affected 26 of 704 (3.7%), and in GGT 127 affected 428 (29.7%).

Discussion. Our (IFNβ-1b) results are similar to another postmarketing study (n = 156; 1 year), which found 37.5% of patients with de novo ALT elevations compared with our 38.9%.[6] In contrast, 11% of patients had mild or moderate ALT elevations in the pivotal clinical trial.[1] Similarly, in an IFNβ-1a(SC) trial (n = 356), ALT was increased in 19.6% and 27.2% of patients treated with low and high doses, which are less than the de novo elevations of 33.6% and 38.0% found in our population.[2] "No evidence of liver enzyme elevations"[3] was reported in the pivotal trial of IFNβ-1a(IM) (n = 158), whereas 23.0% in our study developed de novo elevated ALT ($p < 0.005$ compared with baseline). To better reflect postmarketing experience, a Food and Drug Administration MedWatch warning has since been issued for IFNβ-1a(im) (March 2003) of "hepatic injury including elevated serum hepatic enzyme levels, some of which have been severe." While clinical trials cannot be expected to detect all adverse effects, interpretation of data is hindered by the vague reporting style and use of qualitative rather than quantitative terminology.

The IFNβs differ in their dose, route of administration, glycosylation, amino acid sequencing, formulation pH, excipients, manufacturing, and purifying process. Increasing injection frequency and dose had an effect on subsequent elevated aminotransferases in our population. Dose-dependent hepatotoxicity has been reported with other IFN preparations.[7] Also, increasing the injection frequency without increasing the total dose resulted in more patients with hepatitis C developing elevated ALT.[7] Increased time between injections may enable damaged hepatocytes to recover. Drug-induced hepatotoxicity is complex, and the precise mechanism(s) for many drugs is unknown. The fulminant autoimmune hepatitis found may represent a distinct idiosyncratic reaction.[5] Liver pathology in IFNβ-treated patients with MS is largely unknown; one published biopsy report found "marked portal and lobular inflammation. . .hepatocyte necrosis. . .and mild fibrosis."[8]

No predictors of IFNβ-induced liver injury were found. The preponderance of men with elevated aminotransferases at baseline and during treatment could reflect individual laboratories, of which there were >100, not increasing the ULN for men. The demographic differences found between the IFNβ groups at baseline were not related to subsequent elevated aminotransferases, indicating a negligible effect on results. Other environmental factors, such as concomitant medications, alcohol, and obesity, could compound the risk of IFNβ-induced liver injury. Alcoholic liver disease was unlikely to be an influencing factor in our population because few pa-

tients (3%) had an AST-to-ALT ratio >2. There are no well-documented drug interactions with the IFNβs, although there is potential because IFN inhibits the cytochrome P450 enzymes. Acetaminophen[9] and IV methylprednisolone[10] in combination with IFN can cause elevated aminotransferases.

We suggest regular monitoring of the liver tests, particularly during the first year of treatment, although a balance should be found because frequent testing can cause anxiety, pain, inconvenience, and is not without cost. Patients should be aware of hepatic side effects because even rigorous testing can fail to predict acute liver failure.

Acknowledgment

The authors thank Jon Porciuncula for data entry, Kin Ho for MSCOSTAR information, Dr. Campbell Clark for statistical help, all the neurologists at the MS Clinics for allowing access to their patients, and especially the Vancouver neurologists for contributing to discussions on the work (Drs. V. Devonshire, S. Hashimoto, J. Hooge, L. Kastrukoff, D. Paty, P. Smyth, and T. Traboulsee). The authors also thank the Pharmacy Department, UBC Hospital for helpful discussions and the Special Therapy group and nurses at each clinic (R. Grigg, A. Moore, and A. Springer).

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