ORIGINAL RESEARCH ARTICLE

Drug Safety 2003; 26 (11): 815-827
0114-5916/03/0011-0815/$30.00/0

Hepatic Reactions During Treatment of Multiple Sclerosis with Interferon-β-1a

Incidence and Clinical Significance

Gordon S. Francis,[1] *Yves Grumser*,[1] *Enrica Alteri*,[2] *Alain Micaleff*,[2] *Fanny O'Brien*,[1] *Jonathan Alsop*,[2] *Margaretha Stam Moraga*[2] and *Neil Kaplowitz*[3]

1 Serono Inc., Rockland, Massachusetts, USA
2 Serono International, Geneva, Switzerland
3 USC Keck School of Medicine, University of Southern California Research Center for Liver Diseases, Los Angeles, California, USA

Abstract

Background: Hepatic dysfunction, manifested as liver enzyme elevations, occurs frequently in patients who are treated with interferon, however, data for patients with multiple sclerosis are limited.

Objective: To retrospectively assess the safety profile of interferon-β-1a therapy with respect to liver function during clinical trials and postmarketing surveillance in the treatment of multiple sclerosis.

Patients and Methods: Adverse effects and laboratory abnormalities were analysed from six randomised, controlled clinical trials (five of which were placebo-controlled) that assessed the use of interferon-β-1a in patients with multiple sclerosis. Treatment data were collected for 2819 patients for up to 12 months, of whom 1995 received interferon-β-1a (337 [12%] received Avonex® intramuscular therapy, and 1658 [59%] received Rebif® subcutaneous therapy), and 824 (29%) received placebo. Data for 2 years were collated for 1178 patients (from two studies). Total weekly interferon doses were 22–132μg. Postmarketing surveillance data were also analysed.

Results: In patients receiving interferon-β-1a, there were significant elevations of alanine aminotransferase (ALT) levels, of all grades of severity, in up to 59% of patients at 6 months, up to 64% of patients at 12 months and up to 67% of patients at 24 months; ALT elevations were asymptomatic and dose related. More than 50% of elevations in liver enzymes occurred during the first 3 months of treatment, and more than 75% occurred during the first 6 months. Elevated enzyme levels resolved spontaneously or with dosage adjustment. Although the overall incidence of liver enzyme elevation was high during the early months of therapy, after 2 years, the proportion of patients with abnormal liver enzyme levels was 11% of those receiving Rebif® 44μg three times weekly compared with 6% of placebo-treated patients. Only 0.4% of patients discontinued interferon-β-1a treatment because of hepatic adverse effects. Serious symptomatic

interferon-related hepatic toxicity occurs, but is uncommon. Concomitant medication use was not associated with increased risk.

Conclusion: Asymptomatic hepatic dysfunction is common in patients with multiple sclerosis who are treated with interferon-β-1a, and is dose related. Adverse effects are mainly mild and transient, with little impact on adherence to therapy, although rare serious events can occur. Regular liver function monitoring during the first 6 months is recommended.

Background and Objective

Changes in hepatic function (mainly increases in blood levels of hepatic aminotransferases) occur frequently in patients receiving treatment with type 1 interferon (interferon-α and interferon-β) across all indications.[1] Acute liver failure, defined as a clinical syndrome developing as a result of massive necrosis of hepatocytes or any other cause of sudden and severe impairment of hepatic function, is a rare but well-documented complication of interferon-α treatment of chronic viral hepatitis.[2] It has been reported that liver function alterations occur in 8–38% of patients with relapsing-remitting multiple sclerosis (RRMS) treated with interferon-β in controlled clinical trials,[3-5] or in prospective but non-controlled studies.[6] Most such alterations are asymptomatic and transient biochemical events but symptomatic hepatic dysfunction has been reported in patients receiving interferon-β-1b (Betaseron®,[1] Berlex/Schering)[7] and intramuscular interferon-β-1a (Avonex®, Biogen)[8] therapy for multiple sclerosis. One case of liver transplant has been reported in a patient receiving subcutaneous interferon-β-1a (Rebif®, Serono).[9,10] The patient was also receiving nefazodone (Serzone®, Bristol-Myers Squibb), a drug with known hepatotoxic potential.

Rebif® is a recombinant preparation of interferon-β, produced in Chinese hamster ovary cells. It has an amino acid structure identical to that of native human interferon-β molecule and is glycosylated. Clinical trials have shown that treatment with this interferon-β-1a reduces relapses, disease progression, magnetic resonance imaging (MRI) activity and the burden of disease in patients with RRMS.[4,11] Rebif® also delays the conversion to clinically definite multiple sclerosis in patients with clinically isolated syndromes suggestive of multiple sclerosis,[12] and significantly reduces relapses and MRI activity in patients with secondary progressive multiple sclerosis (SPMS), but does not have a significant impact on disability progression in SPMS patients unless they are still experiencing relapses prior to treatment initiation.[13] The current recommended dosage for Rebif® in RRMS is 44μg subcutaneously three times weekly, although 22μg three times weekly is also available.

In this study, we analysed the data from clinical trials and postmarketing surveillance studies to establish the frequency of liver function abnormalities associated with interferon-β-1a (Rebif® and Avonex®) across a wide range of doses and frequency of administration in patients with multiple sclerosis. The clinical impact of these abnormalities on adherence to therapy was also assessed.

Patients and Methods

We analysed hepatic safety data from a controlled clinical trial database comprising pooled information from six studies that assessed the use of Rebif® in patients with multiple sclerosis for at least 6 months.[4,11-16] Of these studies, five were placebo-controlled and one employed another formulation of interferon-β-1a, Avonex®, at a dosage of 30μg weekly as the comparator.[4,11-16] Data regarding overall treatment discontinuations due to adverse effects were obtained from these studies, including their extension phases (up to 6 years), as well as from 17 other non-controlled multiple sclerosis

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

studies. Information regarding symptomatic liver disease was obtained from Rebif® postmarketing surveillance data.

The database of the six controlled studies included a total of 2819 patients (termed the control population), which comprised a total of 1837 patients with RRMS (from four studies)[4,11,12,14,15] and a total of 982 patients with SPMS (from two studies).[13,16] Treatment data were collected for up to 12 months for the total 2819 patients, of whom 1995 (71%) received interferon-β-1a, (337 [12%] received Avonex® therapy and 1658 [59%] received Rebif® therapy) and 824 (29%) received placebo. Interferon-β-1a was administered to 1396 patients with RRMS and 599 patients with SPMS. Placebo was administered to 441 patients with RRMS and 383 patients with SPMS. The total weekly interferon doses were 22–132μg. Data were collected for 2 years for 1178 patients (from two studies). The 2-year data included 1178 patients (560 with RRMS and 618 with SPMS), of whom 786 were receiving Rebif® and 392 were receiving placebo. The total pooled safety data included information on 4043 patients (total population) with over 7800 patient-years of experience, while the spontaneously reported postmarketing data provided clinical, but not laboratory, information based on approximately 70 000 patients with over 130 000 patient-years of exposure.

Six-month clinical trial data were used to explore dose differences during the initial months on therapy while 1-year and 2-year clinical trial data provided information on later events and recovery using the approved doses (Rebif® 22μg and 44μg three times weekly) for multiple sclerosis.

During the clinical trials, patients were seen by the treating physician at regular visits (weeks 2 and 4, month 3 and then every 3 months). Patients with elevated enzymes in the studies were universally asymptomatic, so that decisions about whether to refer to these enzyme elevations as adverse effects was at the discretion of the unblinded treating physician. As this underestimates the actual impact on liver function, data are presented based on the laboratory data alone. Blood tests for alanine aminotransferase (ALT) levels (also known as serum glutamate pyruvate transaminase [SGPT] levels), aspartate aminotransferase (AST) levels (also known as serum glutamate oxaloacetate transaminase [SGOT] levels), alkaline phosphatase and bilirubin levels were performed at each of the clinical visits. γ-Glutamyl transferase (γ-GT) levels were measured only upon specific request.

For laboratory data, the grading of hepatic dysfunction follows the National Cancer Institute Common Toxicity Criteria, version 2.0, 1998.[17] For ALT, AST, γ-GT and alkaline phosphatase, grade 1 is defined as a value >1 to ≤2.5 × the upper limit of the normal range (ULN), grade 2 is >2.5 to ≤5 × ULN, grade 3 is >5 to ≤20 × ULN, and grade 4 is >20 × ULN. As no grade 4 elevations were seen, and in order to derive more information from the broad range of grade 3, we report the number of patients within this grade who had enzyme elevations of >10 × ULN. For bilirubin, grade 1 exceeds the ULN but is ≤1.5 × ULN, grade 2 is >1.5 to ≤3.0 × ULN, grade 3 is >3.0 to ≤10.0 × ULN and grade 4 is >10 × ULN.

To assess the persistence of liver enzyme elevation, shift tables were prepared that documented the number of patients who had normal, high or low liver enzyme elevations at baseline, cross-correlated with their liver enzyme values at specific timepoints during the study. Persistent new-onset elevations were calculated based on the number of patients with elevated values at the endpoint divided by the number of patients at risk (those with low or normal values) at baseline.

Statistics

The dose-effect of interferon-β-1a on liver function tests was assessed using the Cochran-Armitage trend test. The comparison of proportions affected was analysed using Fisher's Exact test. The 95% CI were estimated using the binomial distribution. All tests were 2-sided expressed to 3 decimal places for results that were statistically significant; otherwise 2 decimal places were used. Values <0.0005 are expressed as $p < 0.001$). Analyses were performed using SAS (version 6.12) and StatXact (version 3.0). The number-needed-to-harm (NNH) and the num-

ber-needed-to-treat (NNT) for benefit were calculated based on the absolute rate increase (ARI) or absolute rate reduction (ARR) using the formula NNH (or NNT) = 1/ARI (or 1/ARR) with 95% CI calculated using exact methods.

Results

Patient Demographics

The ratio of male to female patients was approximately 1 : 2 in the studies of RRMS and 2 : 3 in SPMS. Median (mean) age in the total population was 37 (37.1) years; 35 (35.3) years in patients with RRMS and 44 (43.1) years in those with SPMS. Ninety (90%) of patients were aged between 22–52 years. Patients were predominantly Caucasian.

Incidence of Laboratory Abnormalities

The data for elevated ALT levels in the control population are presented in table I, and indicate that a high proportion of patients had at least one blood test that shows an elevation of enzymes during the period of observation; the proportion increased only minimally beyond 6 months of therapy. Interferon-β-1a-induced hepatic dysfunction was dose related ($p < 0.001$ for dose trend). Figure 1 shows the percentage of patients with at least one abnormal liver enzyme test during the first 6 months by dosage for each of the liver function tests routinely performed.

Severity of Hepatic Disturbance

Abnormal liver function tests from the controlled population, based on severity, are presented in figure 2. Of the patients receiving Rebif® 44μg three times every week, 2.8% (20/727) experienced severe (grade 3) elevations of liver enzymes, of whom two (0.3%) had elevations ranging from 10- to 20-fold greater than the ULN. Of the patients receiving Rebif® 22μg three times weekly, 1.3% (5/398) experienced grade 3 elevations of liver enzymes, one of whom (0.3%) had an elevation more than 10-fold greater than the ULN. One patient (0.3%) receiving Avonex® 30μg once weekly and one pa-

Table I. The percentage of multiple sclerosis patients with symptomatic or asymptomatic elevated alanine aminotransferase (ALT) levels at 6, 12 and 24 months, who were receiving interferon-β-1a (IFNβ-1a)

Time of diagnosis	Cumulative proportion of patients with elevated ALT levels					
	placebo (%) (n = 824)	IFNβ-1a (Rebif®) 22μg once weekly (%) [n = 435]	IFNβ-1a (Avonex®) 30μg once weekly (%) [n = 337]	IFNβ-1a (Rebif®) 44μg once weekly (%) [n = 98]	IFNβ-1a (Rebif®) 22μg three times weekly (%) [n = 398]	IFNβ-1a (Rebif®) 44μg three times weekly (%) [n = 727]
Baseline	10	10	8	7	8	7
6 months	16	28	28	28	44	59[a]
12 months	19	32	38	37	47	64[a]
24 months	26[b]				53	67[c,d]

a $p < 0.001$ for dose trend (Cochran-Armitage trend test).

b n = 392.

c $p = 0.002$; for dose trend (Cochran-Armitage trend test).

d n = 727.

tient (0.1%) receiving placebo had elevations of enzymes that were greater than 10-fold the ULN. Only two patients, both receiving Rebif® 22μg three times weekly, experienced severe (grade 3) elevations of bilirubin; one patient also had grade 2 elevations of ALT levels and the other patient had isolated hyperbilirubinaemia.

Onset and Duration of Elevations of ALT Levels

In the group of patients receiving interferon-β-1a who were followed for 6 months from the controlled population, the median time to onset of elevations in ALT levels ranged from 1.2–2.7 (mean 2.1–2.9) months. There was no clear relationship between dosage and the time to onset. Similar findings were noted for elevated AST levels and bilirubin levels (data not shown), but at lower frequencies. The 2-year patient data showed a median time to onset of 3.0 (mean 8.4) months for placebo, 1.9 (4.4) months for Rebif® 22μg three times weekly and 1.5 (3.0) months for Rebif® 44μg three times weekly. This was consistent with the longer observation period, during which time a small number of new cases would develop and affect the mean, but not necessarily the median time to onset. For patients who were followed for up to 2 years and who developed elevated ALT levels, 59% experienced the onset within 3 months, 72% within 6 months, and 84% within 1 year of starting therapy.

The duration of hepatic adverse effects was examined in patients receiving Rebif® three times weekly for 2 years in order to provide a sufficient observation time after the onset of the event. The median duration of all hepatic adverse effects, including ongoing events at study end, was 90 (mean 139) days in the placebo group, compared with 99 (mean 161) and 120 (mean 176) days in patients receiving Rebif® 22μg three times weekly and Rebif® 44μg three times weekly, respectively. For events judged to have resolved (i.e. not ongoing at the year 2 visit), the median durations were 70, 96 and 113 days, respectively, for patients receiving placebo, Rebif® 22μg three times weekly and Rebif® 44μg three times weekly, respectively. Both methods of examining duration data suggest a dose-response relationship with the duration of adverse effects.

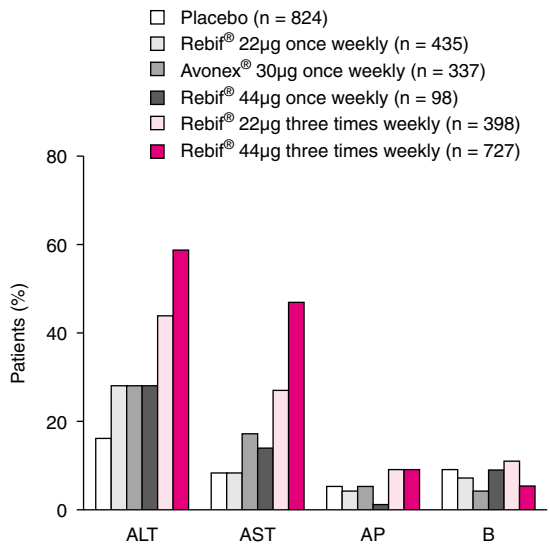

Fig. 1. Percentage of patients with at least one abnormal liver enzyme test during the first 6 months of various dosages of interferon-β-1a therapy. **ALT** = alanine aminotransferase; **AP** = alkaline phosphatase; **AST** = aspartate aminotransferase; **B** = bilirubin.

Resolution of Elevated ALT Levels

The resolution of elevated ALT levels was investigated by examining shift tables, reviewing cases of persistent elevations of ALT levels and the assessment of individual patterns of elevated ALT levels. Shift tables help to compare the proportion of patients, at the end of a specific time interval, who still had abnormal laboratory ALT levels that began during the study compared with the proportion of patients who had abnormal laboratory ALT levels at any time during the study interval. At the end of 1 year, 4.8% (33/686) of placebo-treated patients, 14.1% (49/347) of patients receiving Rebif® 22μg three times weekly and 15% (51/341) of patients receiving Rebif® 44μg three times weekly had abnormal laboratory ALT levels of any grade. After 2 years, the comparable values were 6.5% (22/339), 8.1% (27/334) and 10.9% (36/330), respectively. This demonstrates that, although the proportion of

patients with ALT level elevations at any time during 1 or 2 years was over 60% for those receiving Rebif® 44μg three times weekly (table I), at the end of the interval the proportion of these patients with persistent abnormality of any grade was approximately 10%, which needs to be considered against the backround rate of ALT elevation in untreated patients of 7–10% (table I).

Persistent elevations of ALT levels over consecutive months could best be assessed from the Prevention of Relapses and disability by interferon-β-1a Subcutaneously in Multiple Sclerosis (PRISMS) study, in which patients underwent 4 years of consecutive monitoring.[11] Table II indicates that persistent ALT level elevations were relatively infrequent; 4.1% and 5.5% of patients receiving Rebif® 22μg and 44μg three times weekly, respectively, showed persistent elevations for 1–2 years on therapy, while only 0.6% of patients receiving Rebif® three times weekly had persistent elevations for 4 or

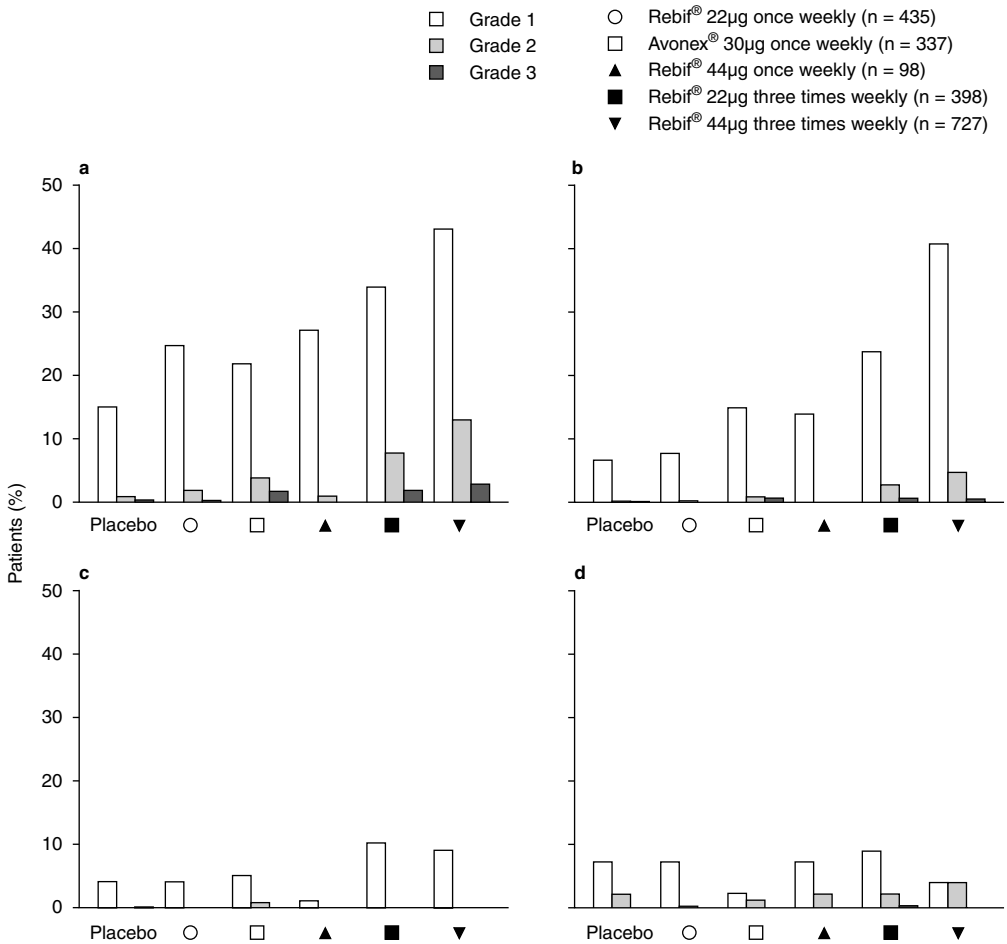

Fig. 2. Percentage of patients with at least one abnormal liver enzyme test (according to severity grade) during the first 6 months of interferon-β-1a (IFNβ-1a) treatment, by total weekly dosage of IFNβ-1a received: (**a**) alanine aminotransferase [ALT], (**b**) aspartate aminotransferase [AST], (**c**) alkaline phosphatase, (**d**) bilirubin. Grade 1 = liver enzyme levels >1 to ≤2.5 × upper limit of the normal range (ULN), grade 2 = levels >2.5 to ≤5 × ULN, grade 3 = levels >5 to ≤20 × ULN (dose effect $p < 0.001$ for ALT and AST, Cochran-Armitage trend test).

Table II. The percentage of relapsing-remitting multiple sclerosis patients with persistent elevation of alanine aminotransferase (ALT) who were receiving interferon-β-1a three times weekly in the PRISMS study[11]

Duration of elevations in ALT levels	Treatment group		
	placebo (n = 187)	Rebif® 22μg three times weekly (%) [n/N][a]	Rebif 44μg three® times weekly (%) [n/N][a]
≥1 but <2 years	0	4.1 (11/271)	5.5 (15/271)
≥2 but <3 years	0	1.8 (5/271)	2.6 (7/271)
≥3 but <4 years	N/A	0.6 (1/167)	0
≥4 years	N/A	0.6 (1/167)	0.6 (1/164)

a Comparisons between interferon dose groups showed no significant difference at any time point, Fisher's Exact Test.

N/A = not applicable (no placebo data available beyond year 2); **n/N** = number of patients with persistent elevation of ALT/total number of patients; **PRISMS =** Prevention of Relapses and disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis.

more years consecutively. All of these patients with chronic elevations of ALT levels were clinically asymptomatic.

ALT level elevations generally resolved spontaneously, or with dose reductions, or interruption of therapy. Detailed data from the EVidence for Interferon Dose-effect: European-North American Comparative Efficacy (EVIDENCE) study[14] showed that 55/339 patients receiving Rebif® 44μg three times weekly developed raised ALT levels to a maximum of grade 2 (n = 44) or grade 3 (n = 11) toxicity at some point during the first 48 weeks of therapy (figure 3). For patients with an onset of grade 2 elevation in whom no dosage adjustments were made (n = 44), 25% of patients (11/44) progressed to grade 3, while 73% (32/44) improved spontaneously without dose adjustment. The remaining patient (2%) fluctuated between grade 1 and 2 but was still grade 2 by study end. All patients who had their doses reduced (n = 11) experienced an improvement in ALT levels. The rate of improvement was not precisely measured as many patients were retested only on their next quarterly visit, particularly those in whom no dosage adjustments were made. Of those with earlier testing, an improvement was seen within 5 weeks of dose modification. Otherwise, an onset of improvement was noted at the next blood test 12 weeks after the abnormality was first detected. Of the 11 patients with grade 3 elevation, four had no dosage change and all four improved, while the remaining seven patients had dosage modifications with improvement in all cases. Dosage re-escalation was attempted in 10 out of 18 patients (grade 2 or 3 patients) who had dose reductions, of whom 9 returned to full dosage. Only two patients had a recurrence of grade 2 toxicity on resuming full dosage (no patients were grade 3) and the drug was stopped in one patient but continued in the second with a spontaneous reduction to grade 1 toxicity.

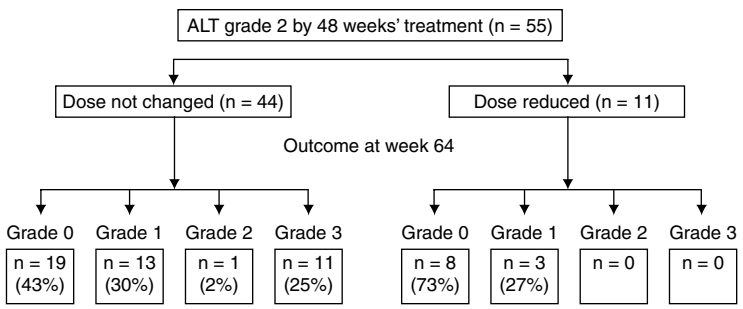

Fig. 3. Resolution of elevations in alanine aminotransferase (ALT) levels during 48 weeks of therapy with subcutaneous interferon-β-1a (Rebif®) 44μg three times weekly in the EVidence for Interferon Dose-effect: European-North American Comparative Efficacy (EVIDENCE) study.[14] Grade 0 = resolution of elevated ALT levels to within the upper limit of the normal range (ULN); grade 1 = levels >1 to ≤2.5 × ULN; grade 2 = levels >2.5 to ≤5 × ULN; grade 3 = levels >5 to ≤20 × ULN.

Similarly, during 2 years of treatment in the PRISMS study, 15 patients (4% of exposed patients) had dosage modifications for abnormal enzymes while receiving Rebif®. In 12 of 13 patients in whom dose reductions were made and in both patients with dose interruptions, there was an improvement of liver enzyme elevations to grade 0 (normal) or grade 1 with dosage modifications. Full doses were re-instituted in 11 of the 13 patients with dose reductions, of whom, normal liver enzyme levels were maintained in seven patients, while four patients experienced repeated elevations. In the two patients in whom the dosage was interrupted, half-dosage was resumed without enzyme elevation.

Treatment Discontinuation

Hepatic abnormalities rarely led to discontinuation of treatment in the controlled population; only eight of 1995 patients receiving active therapy (0.4% of the total population) withdrew from treatment during the first 6 months of therapy. Five patients (three with grade 2 and two with grade 3 elevations) were receiving Rebif® 44μg three times weekly (0.7% of all patients receiving this dosage), two (one grade 2, one grade 3) were receiving Rebif® 22μg weekly (0.5% of all patients receiving 22μg weekly), and one (grade 2 elevation) was receiving Avonex® 30μg once weekly (0.3% of all patients receiving this dosage). The discontinuation of treatment was a result of the elevation of liver enzymes alone in six patients and combined with other events in two patients. Most patients who discontinued treatment did so without trying dose reductions first to determine whether enzyme elevations would abate. Of the total population of patients exposed to either Rebif® or Avonex® (3995), there were 17 treatment discontinuation for enzyme elevations in patients receiving either interferon-β-1a formulations (0.4% of the exposed population) and two in patients receiving placebo (0.2% of the exposed population).

In order to gauge the impact of liver abnormalities in patients with multiple sclerosis receiving interferon-β-1a, we examined the NNH. The outcomes assessed were any elevation in ALT levels, persistent elevation in ALT levels and drug discontinuation related to the elevation in ALT levels for the controlled population. Examining the group receiving Rebif® 44μg three times weekly compared with the placebo group, for any elevation in ALT levels at 2 years the ARI was 41%, with an NNH of 2.4 (95% CI 2.1–2.8, $p < 0.001$), while for persistent elevation at 2 years, the ARI was 4.4%, with an NNH of 23 (95% CI 12–648, $p = 0.054$). For treatment discontinuations related to ALT level elevations at 2 years, the ARI was 0.8%, with an NNH of 129 (95% CI 61–∞ with NNT for benefit = 1017 [not significant], i.e. patients who received the active drug may have a greater or less risk for discontinuation related to ALT level elevations). Comparing Rebif® 44μg three times weekly with Avonex® 30μg once weekly, NNH at 12 months for any elevation in ALT levels (ARI = 24%) for the higher dose regimen (i.e. Rebif®) was 4.1 (95% CI 3.1–5.8, $p < 0.001$), while NNH at 12 months for treatment discontinuations related to elevations in ALT levels (ARI = 0.6%) was 170 (95% CI 57–∞with NNT = 117, $p = 0.62$).

Potential Risk Factors

Gender

In the 6-month dataset, the proportion of patients with ALT level elevations was 67% for men and 31% for women who were receiving Rebif® 22μg three times weekly ($p < 0.001$), 73% for men and 53% for women who were receiving Rebif® 44μg three times weekly ($p < 0.001$), and 22% for men and 13% for women who were receiving placebo ($p = 0.004$). The proportion of men in the dataset was 34%, whereas the proportion of patients with elevated ALT levels who were male was 41%, demonstrating a higher than expected proportion of male patients with elevated ALT levels.

Age

The 6-month data from the controlled population was stratified according to the median age of the population (i.e. younger patients were stratified as <39 years of age, and older patients were stratified as ≥39 years of age). The proportion of patients

receiving Rebif® 22μg three times weekly who had elevated ALT levels during the first 2 years of therapy was 44% in younger patients and 45% in older patients (p = 0.84). The proportion of patients receiving Rebif® 44μg three times weekly who had elevated ALT levels during the first 2 years of therapy was 57% for younger patients and 61% for older patients (p = 0.37). When combining all active treatment groups, 39% of patients <39 years of age developed elevated ALT levels during the first 6 months of therapy compared with 46% of patients ≥39 years of age (p = 0.001). For patients receiving placebo, 16% of young patients and 17% of older patients had elevated ALT levels (p = 0.57).

Concomitant Medications

Concomitant medications may contribute to hepatic toxicity. In the controlled population (2819 patients), a number of concomitant medications that may interact with interferon-β-1a were explored, including paracetamol (acetaminophen) [721 concomitant exposures], propionic acid derivatives such as ibuprofen (336 concomitant exposures), non-selective monoamine oxidase inhibitors (195 concomitant exposures), selective serotonin re-uptake inhibitors (184 concomitant exposures), opioids (176 concomitant exposures), baclofen (176 concomitant exposures), antiepileptic medications (121 concomitant exposures), amantadine (77 concomitant exposures), acetic acid derivatives (64 concomitant exposures), nefazodone (52 concomitant exposures), tizanidine (25 concomitant exposures), pemoline (25 concomitant exposures), cyclo-oxygenase inhibitors (20 concomitant exposures), and dantrolene (17 concomitant exposures). The proportion of patients with elevated liver enzymes during 2 years of interferon-β-1a therapy who were taking a concomitant medication were compared with those who were not taking a concomitant medication. Patients were grouped as low exposure (<66μg per week; Rebif® or Avonex®) and high exposure (>66μg per week [Rebif®]). In general, there was no evidence of an increase in the proportion of patients with liver enzyme elevation when taking any of the above medications together with interferon-β-1a therapy.

Table III provides information on propionic acid derivatives or paracetamol taken concomitantly with interferon-β-1a and the relative proportions of patients with elevated liver enzymes. Concomitant use of paracetamol is associated with a significantly lower risk of hepatic dysfunction than the use of interferon alone (absolute risk reduction = 7%; 95% CI 3–12%; p < 0.005). This reduced risk is also seen in patients receiving paracetamol concomitantly with placebo. The only concomitant medication class that was associated with a significantly increased risk of liver dysfunction was propionic acid derivatives, such as naproxen, ibuprofen, and indomethacin (absolute risk increase = 16%; 95% CI 11–20%; p < 0.001). However, the risk is also increased when medications of this drug class are given concomitantly with placebo, which suggests that the increased risk is associated with the use of propionic acid derivatives and not with interferon-β-1a, *per se*.

Weight

Some debate exists as to whether patient bodyweight will affect adverse effect rates, with the hypothesis that smaller patients may be more at risk for adverse effects. To determine whether weight had any effect on liver toxicity in the controlled population during 2 years of interferon-β-1a therapy, patients were stratified above or below a value close to the median weight of the population (which was 66kg; 52% of patients were ≥66kg and 48% of patients were <66kg). More patients with elevated ALT levels were ≥66kg (62%) rather than <66kg (38%), indicating that lower bodyweight does not necessarily predispose patients to a greater risk of liver enzyme elevation.

Postmarketing Experience

During postmarketing surveillance, involving approximately 70 000 patients over 5 years, 30 serious cases (as defined by ICH E2A)[18] of symptomatic liver dysfunction have been reported. Approximately half (n = 15) of the 30 patients had reported jaundice, while the remainder either did not have jaundice (25%) or insufficient information was available to determine the presence or absence of jaundice (25%). ALT levels were increased in all

Table III. Use of concomitant medication with interferon-β-1a (IFNβ-1a) and the risk of alanine aminotransferase (ALT) elevation

Concomitant medication	IFNβ-1a dose	Percentage of patients with elevated ALT levels		Percentage difference based on receiving, or not receiving, concomitant medication (95% CI)	Odds ratio	p-Value[a]
		patients receiving concomitant medication (*n*/N)	patients not receiving concomitant medication (*n*/N)			
Propionic acid derivatives	High[b]	63 (600/956)	47 (157/336)	16 (10–22)	1.9	<0.001
	Low[c]	39 (280/724)	24 (62/260)	15 (9–21)	2.0	<0.001
	Placebo	25 (184/727)	14 (12/89)	12 (4–20)	2.2	0.012
	Both high and low groups combined	52 (880/1680)	37 (219/596)	16 (11–20)	1.9	<0.001
Paracetamol	High[b]	55 (398/721)	63 (359/571)	8 (2–13)	0.7	0.006
	Low[c]	30 (146/492)	40 (196/492)	10 (4–16)	0.6	0.001
	Placebo	17 (61/356)	29 (135/460)	12 (7–18)	0.5	<0.001
	Both high and low groups combined	45 (544/1213)	52 (555/1063)	7 (3–12)	0.8	0.005

a p-Value calculated from Fisher's Exact test.

b High = IFNβ-1a >66μg per week.

c Low = IFNβ-1a 1–66μg per week.

n/N = number of patients with persistent elevation of ALT/total number of patients.

patients; the amount of increase ranged from 6-fold to almost 100-fold above normal. AST levels were similarly elevated. In those with elevated bilirubin, values were increased 2-fold to 35-fold. γ-GT values were measured in 60% of these patients and were elevated in all but one patient; the extent to which γ-GT levels were increased was usually less than that of ALT levels. Elevations of international normalised ratios were reported in six patients. Of the 30 patients with severe hepatic dysfunction in the post-marketing surveillance, it was found that 26 (90%) were women. No other specific risk factors were identified, although data on medical history, concomitant medication and alcohol history were scant. No single concomitant medication was used in more than 25% of patients. Two patients received liver transplantation although only one patient was encephalopathic; the patient whose case was published[9] was also exposed to another potentially hepatotoxic product[10,19] while no potential confounders were noted in the second patient.

While recognising the limitations of postmarketing data, with approximately 70 000 exposed patients and 130 000 patient-years, the rate of serious symptomatic cases is approximately 1/2300 patients or 1/4000 patient-years' exposure. No specific guidance, other than cessation of interferon therapy, is available. Almost all cases resolved despite severe liver abnormalities.

Discussion

The clinical trial data presented show that the elevation of hepatic aminotransferase is common during the first 12 months of treatment of multiple sclerosis with interferon-β-1a, with up to 59% of patients receiving Rebif® 44μg three times weekly and almost 40% receiving Avonex® 30μg weekly experiencing elevated ALT levels. More than 50% of enzyme elevations developed within the first 3 months of treatment and 75% within 6 months although late onset cases (up to 2 years after the initiation of therapy) were seen infrequently. The overall clinical impact of liver dysfunction is relatively minor. Dosage reductions are necessary in less than 5% of treated patients; the vast majority of

hepatic enzyme elevation events were asymptomatic, most events remitted spontaneously while on therapy, and dose modifications universally led to a decrease in liver enzyme values. However, more severe symptomatic cases have been reported with marketed interferon-β-1a products, including two cases of liver transplant. The estimated incidence of the symptomatic events associated with interferon-β-1a is approximately 1 per 2300 treated patients or, based on total exposure, one per 4000 patient-years. Calculations such as these, however, need to be tempered by the fact that postmarketing data provide imprecise estimates of total exposure and reported events.

All of the data presented relate to interferon-β-1a, with the majority related to one specific formulation (Rebif®) and fewer data regarding the alternative regimen (Avonex®). However, hepatic dysfunction is not an adverse effect specific to interferon-β-1a but rather is an interferon class effect. Liver disorders have also been reported in patients treated with other type 1 interferons, including patients with multiple sclerosis treated with interferon-β-1b.[7] A retrospective 1-year study in 156 patients with RRMS,[6] all of whom were treated for the first time with interferon-β-1b (8×10^6 IU every alternate day), found alterations in liver function in 4.6% of patients at baseline and 37.5% during interferon-β-1b treatment. The probability of having altered liver function was highest at months 3 and 6, with values returning to levels similar to baseline by month 9. These results suggest that there is a probable causal relationship between starting interferon-β-1b treatment and the occurrence of altered liver function. However, as with interferon-β-1a, the alterations were mostly mild and transient.

The pathophysiological mechanisms of hepatotoxicity during interferon-β-1a treatment are not fully understood. Interferon-β-1a has direct toxic effects on hepatocytes, leading to changes in protein synthesis and ultrastructure.[20] Other cytokines induced by interferon-β-1a might also cause hepatocyte damage. Interferon-β-1a depresses the activity of inducible and constitutive cytochrome P-450 isoenzymes,[21] and the activity of drug-metabolising enzymes.[22] Hence, a potentiating effect on the toxicity of other drugs cannot be ruled out although no relationship of liver injury to the use of other drugs concomitantly could be detected in this database. Of specific interest in relation to interferon therapy in multiple sclerosis is that patients are advised to use paracetamol either as prophylaxis or as symptomatic therapy for interferon-induced flu-like symptoms. The recommended doses of paracetamol are not sufficient to cause liver damage alone but it is possible that long-term use of paracetamol may deplete glutathione stores, rendering hepatocytes vulnerable to the effect of cytokines such as interferon. However, the data in the present study assessing the use of paracetamol in conjunction with interferon-β-1a do not indicate an increased risk of hepatic dysfunction with this medication combination.

It has also been suggested that the action of interferon-β-1a may induce or unmask autoimmune hepatitis, although this mechanism has been considered unlikely because liver dysfunction while taking interferon-β-1b was rarely associated with non-organ-specific autoantibody positivity.[6] The higher prevalence of asymptomatic enzyme elevation in men than in women in this pooled clinical trial data, in contrast to a very high proportion of symptomatic cases in women, and coupled with the known predominance of autoimmune hepatitis in women,[23] raises the possibility that different mechanisms of injury operate in the two situations. Cytokine-related toxicity plus other unidentified factors may be responsible for asymptomatic elevation of ALT levels, while drug-induced autoimmune injury may be a more relevant factor in symptomatic patients.

A search for risk factors in the current study found that only the asymptomatic elevations of hepatic enzymes were more common in men than in women, although a similar gender trend was noted in placebo-treated patients. Older patients were also more likely to develop elevated ALT levels than younger patients, but no clear relationship to the use of other medications or characteristics of the underlying disease was apparent.

Based on the clinical trial data for Rebif® at doses of 22 or 44μg three times weekly, it is recom-

mended that liver function tests should be performed before commencing treatment and repeated at months 1, 3 and 6, and at regular intervals thereafter, as needed. Continued monitoring will enable the detection of infrequent cases of liver dysfunction developing 2 years or more after the start of therapy. Elevations of liver enzymes during treatment should be managed as follows:

- for patients with grade 4 toxicity (>20 times the ULN) or jaundice, interferon-β should be discontinued permanently;
- for patients who develop grade 3 toxicity (>5 times the ULN), the dose of interferon-β should be reduced, or interrupted and cautiously reinstated when enzymes return to normal or to grade 1 toxicity (less than 2.5 times the ULN);
- for patients who develop recurrent grade 3 toxicity, the dose of interferon-β should be permanently reduced or treatment should be discontinued;
- patients who develop grade 2 toxicity should be closely monitored, or managed in a similar manner to those with grade 3 toxicity.

It remains unproved however, that such monitoring will detect or prevent the more serious symptomatic cases,[24] often occurring with rapid onset. Patient education to recognise symptoms is important as is immediate cessation of therapy in a patient presenting with jaundice.

When using any product, a benefit-risk assessment is important. While recognising the impact on safety of higher doses of interferon, there is substantial evidence that the beneficial effects of interferon-β-1a in multiple sclerosis are also related to dose and/or frequency of administration,[25] and in a recent direct comparison of subcutaneous Rebif® 44μg three times weekly versus intramuscular Avonex® 30μg once weekly, the Rebif® regimen was superior in both relapse and MRI measures.[14] Clinicians need to weigh the superior efficacy of higher and more frequent dosages with Rebif® compared with low-dose therapy on disease measures (NNT = 10 [95% CI 8–13, $p < 0.001$] to avoid a relapse) against the impact of dose-related risks of hepatic dysfunction (NNH = 4 for asymptomatic elevation of enzymes or NNH = 170 for treatment discontinuation due to elevated enzymes) on patient tolerance and adherence to therapy.

Much remains to be learned about the actions of interferon on the liver. However, it is clear that there is a potential for toxicity when patients with multiple sclerosis are treated with interferon-β, including rare life-threatening reactions, and it is recommended that the monitoring regimen outlined in this section be adopted for all patients with multiple sclerosis commencing therapy with interferon-β.

Acknowledgements

The authors wish to express thanks to the patients who have participated in the studies, contributing data to this analysis, and to the physicians and other study site personnel responsible for their care. Studies from which data have been utilised include PRISMS, SPECTRIMS, ETOMS, OWIMS, Nordic SPMS and EVIDENCE. Jennie Corrigan and Sarah-Jane Blake, Caudex Medical, provided valuable manuscript assistance.

Drs Francis, Grumser, Alteri, Micaleff, O'Brien, Alsop and Stam Moraga are employees of Serono. Dr Kaplowitz has provided consulting services to Serono.

References

1. Vial T, Descotes J. Clinical toxicity of the interferons. Drug Saf 1994; 10 (2): 115-50
2. Durand JM, Kaplanski G, Portal I, et al. Liver failure due to recombinant alpha interferon. Lancet 1991; 338: 1268-9
3. IFNB Multiple Sclerosis Study Group. Interferon-beta-1b is effective in relapsing-remitting multiple sclerosis: I. clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43: 655-61
4. PRISMS (Prevention of Relapses and disability by interferon-beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomized double-blind placebo-controlled study of interferon-beta-1a in relapsing/remitting multiple sclerosis. Lancet 1998; 352: 1498-504
5. Durelli L, Ferrero B, Oggero A, et al. Autoimmune events during interferon-beta-1b treatment for multiple sclerosis. J Neurol Sci 1999; 162: 74-83
6. Durelli L, Ferrero B, Oggero A, et al. Liver and thyroid function and autoimmunity during interferon-beta1b treatment for MS. Neurology 2001; 57: 1363-70
7. Durelli L, Bongioanni MR, Ferrero B, et al. Interferon treatment for multiple sclerosis: autoimmune complications may be lethal. Neurology 1998; 50: 570-1
8. Duchini A. Autoimmune hepatitis and interferon-beta-1a for multiple sclerosis. Am J Gastroenterol 2002; 97: 767-8
9. Yoshida EM, Rasmussen SL, Steinbrecher UP, et al. Fulminant liver failure during interferon-beta treatment of multiple sclerosis. Neurology 2001; 56: 1416
10. Yoshida EM, Rasmussen SL, Steinbrecher UP, et al. Correction: fulminant liver failure during interferon-beta treatment of multiple sclerosis. Neurology 2001; 57: 2153

11. PRISMS (Prevention of Relapses and disability by interferon-beta-1a Subcutaneously in Multiple Sclerosis) Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: long-term efficacy of interferon-beta-1a in relapsing MS. Neurology 2001; 56: 1628-36

12. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomized study. Lancet 2001; 357: 1576-82

13. SPECTRIMS Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: clinical results. Neurology 2001; 56: 1496-504

14. Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon-β-1a treatment regimens in MS: The EVIDENCE Trial. Neurology 2002; 59: 1496-506

15. Once Weekly Interferon for MS Study Group. Evidence of interferon-beta-1a dose response in relapsing-remitting MS: the OWIMS Study. Neurology 1999; 53: 679-86

16. Andersen O, Elovaara E, Farkkila M, et al. Multicentre, randomized, double-blind, placebo-controlled phase II study of weekly, low dose, subcutaneous interferon-beta-1a in secondary progressive multiple sclerosis (SPMS). J Neurol Neurosurg Psychiatry 2003. In press

17. National Cancer Institute Common Toxicity Criteria, version 2.0, 1998 [online]. http://www.ctep.cancer.gov/reporting/ctc.html [Accessed 2003 Jul]

18. ICH Harmonised Tripartite Guidelines [online]. Available from URL: http://www.ich.org/pdfICH/e2a.pdf [Accessed 2003 Jul]

19. Aranda-Michel J, Koehler A, Bejarano PA, et al. Nefazodone-induced liver failure: report of three cases. Ann Intern Med 1999; 130: 285-8

20. Itoh S, Marutani K, Matsuo S. Changes in ultrastructure of hepatocytes and liver test results before, during, and after treatment with interferon-beta in patients with HB(e) Ag-positive chronic active hepatitis. Dig Dis Sci 1992; 37: 1260-7

21. Carelli M, Porras MC, Rizzardini M, et al. Modulation of constitutive and inducible hepatic cytochrome(s) P-450 by interferon-beta in mice. J Hepatol 1996; 24: 230-7

22. Okuno H, Takasu M, Kano H, et al. Depression of drug-metabolizing activity in the human liver by interferon-beta. Hepatology 1993; 17: 65-9

23. Krawit EL. Autoimmune hepatitis. N Engl J Med 1996; 334: 879-903

24. Kaplowitz N. Drug-induced liver disorders. Implications for drug development and regulation. Drug Saf 2001; 24 (7): 483-90

25. Goodin DS, Frohman EM, Garmany Jr JP, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002; 58: 169-78

Correspondence and offprints: Dr *Gordon S. Francis*, One Technology Park, Rockland, MA 02370, USA.
E-mail: gordon.francis@serono.com