

## SLCO1B1 Variants and Statin-Induced Myopathy

**TO THE EDITOR:** Investigators in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group found one single-nucleotide polymorphism (SNP) in the *SLCO1B1* gene that was significantly associated with the risk of development of statin-induced myopathy ( $P=4\times 10^{-9}$ ) (Aug. 21 issue).<sup>1</sup> The study was performed in patients with a history of myocardial infarction taking a high dose (80 mg) of simvastatin.

The investigators evaluated other SNPs that have been reported elsewhere as having an association with statin myopathy but could not confirm any significant association in these cases. In our investigation of mutations in 110 patients with severe statin-induced myopathy,<sup>2</sup> we found that disease-causing mutations in the gene associated with McArdle's disease (*PYGM*) and in the carnitine palmitoyltransferase II gene (*CPT2*) increased by factors of 20 and 13, respectively. Both mutations were of low frequency — 1 in 340

alleles for *PYGM* and 1 in 540 alleles for *CPT2*. Known SNPs of high frequency in the *PYGM* and *CPT2* genes that have been associated with a low relative risk of muscle disease were also evaluated by the SEARCH group, which found no association with statin-induced myopathy. This is not a surprising finding considering the low-frequency disease-causing mutations we found to be associated with statin-induced myopathy that could not be effectively captured by the common SNPs examined by the SEARCH group.

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## Hepatitis B Virus Infection

**TO THE EDITOR:** In his review article on drug therapy for hepatitis B virus (HBV) infection, Dienstag (Oct. 2 issue)<sup>1</sup> does not mention the use of prophylactic antiviral drugs in patients treated with chemotherapy, stem-cell transplantation, or immunosuppressive agents. Reactivation of hepatitis B (including death<sup>2</sup>) has been described in patients who were anti-hepatitis B core-positive and hepatitis B surface antigen (HBsAg)-negative.<sup>3</sup> Several guidelines and discussions<sup>4,5</sup> on this topic have been published, recommending lamivudine as prophylaxis. This is an important issue that should have been included in the review article because there is an increasing population of patients who are at risk for this threatening complication.

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**TO THE EDITOR:** We believe it would be relevant to stress that nucleotide and nucleoside analogues can prevent HBV reactivation in patients undergoing immunosuppression who have either inactive disease (HBsAg-positive, hepatitis B e antigen [HBeAg]-negative, anti-HBe-positive, normal aminotransferase levels, HBV DNA of <20,000 IU per milliliter, and anti-hepatitis B core IgM-negative) or occult disease (HBsAg-negative, with markers of previous HBV contact [i.e., isolated hepatitis B core antigen]).<sup>1</sup> HBV reactivation is a known

and feared complication in patients who are undergoing immunosuppressive regimens that favor viral replication and, consequently, widespread hepatocyte infection. After immunocompetence is regained, immunomediated hepatic damage develops, leading to acute hepatitis or hepatic failure.<sup>2</sup> Reactivation has also been described in patients receiving immunosuppressive agents such as glucocorticoids, azathioprine, and infliximab in various clinical settings (gastroenterology, dermatology, oncology, and rheumatology).<sup>1</sup> Preemptive treatment with nucleotide and nucleoside analogues effectively reduces the risk of HBV reactivation in hematology patients,<sup>3</sup> even if protocols and the issue of treating occult carriers are still debated.<sup>4</sup> The search for inactive or occult HBV infection should be mandatory in all patients undergoing immunosuppression, since effective prophylaxis is now available.

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**TO THE EDITOR:** In his report on the worldwide prevalence of HBV infection, Dienstag places Italy among countries with a medium endemic level (defined as a prevalence of HBsAg of >2%). Actually, the epidemiology of HBV infection has changed markedly in Italy during the past three decades. In the early 1980s, Italy was a country with a medium endemic level, with an HBsAg prevalence of 3.4%. The prevalence dropped to 1.6% in 1990.<sup>1</sup> Currently, Italy is at a very low endemic level, with an HBsAg prevalence of less than 1%, as clearly stated by some surveys, which were performed from 1994 through 2008 (Table 1).<sup>2,3</sup> At the same time, a decrease in the prevalence of HBeAg and hepatitis delta positivity was observed among HBV carriers.

**Table 1. Prevalence of Hepatitis B Surface Antigen (HBsAg) in Italy, According to Recent Surveys.**

Year	No. of Subjects	Prevalence of HBsAg		Study
		%		
2006	1540	0.9		Da Villa et al. <sup>2</sup>
2008	965	1		Fabris et al. <sup>3</sup>

Since 1991, HBV vaccination has been mandatory in Italy for all newborns and adolescents, and coverage of 94% has been reached. According to the National Surveillance System, the incidence of acute HBV infection per 100,000 inhabitants declined from 5.1 in 1991 to 1.3 in 2005.<sup>4</sup>

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**THE AUTHOR REPLIES:** Bergua et al. and Marignani et al. point out the importance of beginning antiviral therapy preemptively in patients with HBV infection (whether active, inactive, or even recovered) who undergo immunosuppressive chemotherapy, without which HBV reactivation can result in substantial morbidity and mortality. My brief review of antiviral therapy for HBV infection had space constraints, which prevented me from addressing the topic of patients with therapeutic immunosuppression, as well as other special populations (e.g., children, pregnant women, organ-allograft recipients, and patients with renal failure or extrahepatic disease). For a thorough overview of antiviral therapy in these specific populations in general and in immunosuppressed patients in particular, readers should consult comprehensive practice guidelines issued by national organizations,<sup>1,2</sup> as well as the October 2008 proceedings

of the National Institutes of Health Consensus Development Conference on Management of Hepatitis B.<sup>3</sup>

I thank Milazzo and Antinori for pointing out the declining prevalence of HBV infection in Italy, a pattern evolving in other countries with either a low or moderate prevalence during the contemporary era of HBV vaccination. My intent in showing the world map of HBV prevalence was to emphasize the difference in clinical expression of HBV infection on the basis of the time in life when the infection is acquired. This factor, in turn, is a reflection of the prevalence of the infection in the general population, with a high prevalence in countries in which there is primarily perinatal infection and a low prevalence in countries in which there is primarily adult infection. I was not able to update the current world map on a country-by-country basis and relied instead on data in the public domain derived from the Centers for Disease Control and Prevention (CDC).<sup>4</sup> On September 19, 2008, 2 weeks before the publication of my article in the *Journal*, the CDC published an updated world map showing

the prevalence of HBV infection, in which Italy was categorized as a low-prevalence country.<sup>5</sup> A corrected version of the world map in my article, which also corrects other areas in western and northern Europe, is available at NEJM.org.

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## An $\alpha$ -Melanocyte-Stimulating Hormone Analogue in Erythropoietic Protoporphyrin

**TO THE EDITOR:** Patients with erythropoietic protoporphyria, a rare inherited disease, accumulate photosensitizing protoporphyrin in the dermis, which results in severe dermal pain and incapacitating phototoxic reactions when the skin is exposed to visible light, primarily blue light (the Soret band, with the strongest absorbance among the porphyrins).<sup>1</sup> Current treatments are partially effective at best (unpublished data). A beneficial effect of melanogenesis induced by natural sunlight or by ultraviolet radiation has been described in anecdotal reports.<sup>2,3</sup>

Afamelanotide (Nle<sup>4</sup>-D-Phe<sup>7</sup>- $\alpha$ -melanocyte-stimulating hormone, formerly called CUV1647) is an  $\alpha$ -melanocyte-stimulating hormone analogue that induces epidermal melanin formation.<sup>4</sup> Here, we describe the responses of five patients with erythropoietic protoporphyria to a sustained-release resorbable implant formulation of afamelanotide, administered subcutaneously at a dose of 20 mg, given twice, at an interval of 60 days

(in a phase 2 open-label study). Tolerance to standardized xenon-light irradiation measured on the dorsum of the hand was the primary end point. Secondary end points were related to the duration of sunlight exposure tolerated, severity of pain related to erythropoietic protoporphyria, and adverse effects as recorded in diaries, as well as melanin density measured with the use of reflectometry, the quality of life as measured on the 36-item Short-Form General Health Survey (SF-36), and results of biochemical monitoring (as a measure of safety).

Both tolerance to artificial light and melanin density increased significantly by day 120 after the start of afamelanotide, to 11 times and 1.3 times the baseline values, respectively ( $P=0.004$  and  $P=0.007$ ) (Fig. 1). The increase in time to a response to artificial light did not correlate with the increases in melanin density but was dependent on the  $\log_{10}$  baseline response time (data not shown). We speculate that interindividual