patients with PTLD in both studies is small (6 in the study of Hezode et al. and 13 in our study) increasing the probability of type 2 statistical error. The distribution of underlying liver diseases before transplantation is different between the two studies with a larger percent of patients transplanted for HCV-related cirrhosis in the study by Hezode et al. compared with a larger percent of patients transplanted for cholestatic liver diseases in our study. Viral factors including the HCV genotype and HCV RNA titers may also play a role and may have been different between the two populations. Finally, host-related factors such as genetic predisposition may potentially be important for the development of PTLD in the setting of HCV infection. Host predisposition may also explain discrepancies found in the literature related to HCV infection and B-cell non-Hodgkin's lymphoma in immunocompetent patients with chronic HCV. Although studies from Italy[2,3] and the United States[4] (Hispanic population) suggested a link between HCV and B-cell lymphomas, two reports from the United Kingdom[5,6] failed to demonstrate it.

In conclusion, we propose that more studies are needed before PTLD can be listed as one of the extrahepatic manifestations of HCV infection in liver transplant recipients.

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Reply:

We read with interest the report from Zein et al. showing no increased incidence of B-cell non-Hodgkin's lymphomas (B-NHLs) in patients transplanted for hepatitis C virus (HCV)-related cirrhosis in their center, a finding in contrast with our own results.[1] As noted from many previous reports, this discrepancy illustrates the complexity of the relationship between HCV infection and B-NHLs. From the various published series, it appears that HCV is associated with a moderate, but significant increase in the incidence of B-NHLs in certain groups of patients, but not in others. What differentiates these groups of patients remains unknown. In this context, the hypotheses raised by Zein et al. to explain the discrepancy between their results and ours should certainly be considered, together with the role of additional factors, such as the genetic background of the patients, cofactors of various natures, or immunosuppressive therapy, which is not described in Zein's study and might consistently differ from that administered to our patients. Overall, based on the published data, the following consensus can probably be reached: HCV is not the main etiologic agent of B-NHL; B-NHL is likely a multifactorial disease; nevertheless, HCV might play a role in certain forms of B-NHLs in certain groups of patients, through mechanisms we recently discussed.[2] It is therefore obvious that further epidemiological studies are needed in which both the type of B-NHL and the population of the study are carefully described, together with further basic studies exploring the oncogenic potential of HCV, its interactions with other factors involved in B-NHLs such as, for instance, Epstein-Barr virus infection, and the role of host factors.

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Carvedilol—A New Nonselective Beta Blocker

To the Editor:

We read with interest the article by Bañares et al.,[1] which compared in patients with cirrhosis the acute hemodynamic effects of a vasodilating beta blocker, carvedilol, with that of propranolol. We have previously shown a similar acute portal pressure lowering effect of carvedilol in such patients, although in contrast to Bañares et al., we did not identify any significant difference in azygos vein or hepatic bloodflow.[2] In addition, we have also shown that this portal hypotensive effect is maintained after 4 weeks of continuous treatment with carvedilol 25 mg/d.[3]

However, despite the potent portal hypotensive action of carvedilol, we feel that this drug should be used with caution in patients with cirrhosis particularly in view of its tendency to cause systemic hypotension. As we reported in our acute study, 1 patient experienced a profound hypotensive event 105 minutes after the administration of 25 mg

carvedilol. Within the 4 weeks of our continuous treatment study, 7 of 17 patients withdrew, 3 for reasons of hypotension. In addition, 1 further patient required a reduction in dose of carvedilol to 12.5 mg. Bañares et al. do not describe any specific hypotensive events, but the mean percentage decrease in mean arterial pressure of 17.2% described in their study was greater than the 10.5% reduction we noted acutely.

A problem of using carvedilol in a population of patients with chronic liver disease is the potential for significant interindividual bioavailability of the R(+) and S(−) enantiomers of the drug. The S(−) enantiomer has nonselective β-adrenoceptor antagonism, whilst both the S(−) and R(+) enantiomer have approximately equal α_1-adrenoceptor antagonism.[4] In healthy patients stereoselective first pass metabolism leads to the R(+) enantiomer having twice the bioavailability of the S(−) enantiomer.[5] However, patients with cirrhosis have increased and relatively equal bioavailability of both enantiomers.[6] Thus, patients with greater impairment of liver function might experience greater β-adrenoceptor antagonism. In addition, the R(+) enantiomer may exhibit preferential renal clearance.[6] Thus, patients with ascites who commonly have renal impairment might experience greater α_1-adrenoceptor antagonism through the R(+) enantiomer. We have observed a greater decrease in the diastolic blood pressure of those patients with ascites after the acute administration of 25 mg carvedilol. In addition, 2 of the 3 patients who had to withdraw from the 4-week study because of hypotension had ascites.

In conclusion, while carvedilol has potent portal hypotensive properties, its unpredictable bioavailability in a population of patients with poor liver function and possible renal impairment make it less than ideal for the prevention of variceal hemorrhage. It should be used with caution on account of its potential for systemic hypotension.

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Reply:

We thank Drs. Forrest, Stanley, and Hayes for their kind comments on our report on the acute hemodynamic effects of carvedilol in patients with cirrhosis.[1] We are aware of their studies on carvedilol. We actually quoted their initial study (our reference 33) and noted their finding that carvedilol did not decrease renal vein blood flow in 10 patients with cirrhosis. We did not comment on the apparent lack of effects of carvedilol on azygos blood flow and hepatic blood flow because of the very small number of patients studied (6 and 5), which makes possible a type-2 error, especially in view of the lack of a control group. Indeed, this is the likely explanation for the discrepancy with our findings, because our study included these measurements in 14 patients given carvedilol, 14 receiving propranolol, and 7 receiving placebo. The reduction of azygos blood flow caused by carvedilol was statistically significant with respect to placebo (but not from those of propranolol) even when applying the Bonferroni correction for multiple comparisons.

In the letter by Forrest et al., they point out that despite its potent portal hypotensive effects, carvedilol should be used with extreme caution because of its tendency to cause systemic hypotension. We entirely agree. Because of that, almost half of our discussion was devoted to this important caveat.[2] Indeed, the conclusion of the report and of the abstract ended with a strong word of caution on this potentially serious adverse effect, which calls for careful evaluation before the long-term use of carvedilol for portal hypertension could be considered. As in their experience, symptomatic hypotension was noted in 1 of our patients in the acute administration study.

Regarding the chronic administration of carvedilol, the high incidence of drug withdrawal quoted by Dr. Forrest (7 of 17 patients) is much higher than expected even in patients with advanced cirrhosis. It should be noted that the same group has recently reported an unexpected high rate of drug withdrawal (24 of 66 patients) in patients receiving propranolol.[3] Such a poor tolerance may be related, at least in part, to the mode of drug administration, involving long-acting propranolol instead of the recommended individual titration against changes in heart rate and arterial pressure.[4] With carvedilol, as noted in our study, it is strongly recommended to filter the dose of carvedilol, starting as low as 3.125 mg twice daily, as is recommended for patients with heart failure.[5] Individual adjustment of the dose will minimize the risk of excessive beta or alpha 1 blockade because of differences in the bioavailability of the R(+) and S(−) enantiomers of carvedilol. In fact, using this cautious approach, only 3 of 26 cirrhotic patients were intolerant in a prospective study to assess the long-term effects of carvedilol on splanchnic and systemic hemodynamics, renal function, and endogenous vasoactive systems.

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Hepatitis C and Autoimmune Hepatitis

To the Editor:

In their review, Cerny and Chisari[1] postulate a relationship between hepatitis C and autoimmune hepatitis, based on molecular mimicry involving the hepatitis C virus (HCV) core sequence and cytochrome P450 2A6 and 2A7. They refer to a report by Kammer et al. that has now been published.[2] I would like to raise a few issues.

Hepatitis C does not cause autoimmune hepatitis type 2. The fact is that LKM-1 antibodies, the serological marker of autoimmune hepatitis type 2 reacting with cytochrome P450 2D6, are also found in a small proportion of patients with chronic hepatitis C (0%-7%). The targets of LKM-1 antibodies in hepatitis C infection are cytochrome P450 2D6, in particular conformational epitopes, and other as yet unidentified microsomal proteins of 59 kd and 70 kd. Kammer et al.[2] found that cytotoxic T cells specifically respond to the HCV core derived synthetic peptide (LLALLSCLTV). In some cases cytochrome P450 2A6 8-17 (LVALLVCLTV) and cytochrome P450 2A7 8-17 (LVALLACLTV) are also recognized. Cerny and Chisari conclude that molecular mimicry may thus be operative at the level of CD8-positive MHC class I restricted T cells potentially leading to autoimmunity.

Cytochrome P450 2A6 is not an autoantibody target in autoimmune hepatitis type 2. It is a major target in the autoimmune polyendocrine syndrome type 1, a genetically determined multiorgan endocrine disorder caused by mutations in a transcription factor named AIRE. A minority of patients with chronic hepatitis C also expresses humoral antibodies against cytochrome P450 2A6. Although the hypothesis of molecular mimicry between hepatotropic viruses and the induction of autoimmunity is very attractive and has been followed by our group for years, the data provided by Kammer et al. do not support this hypothesis. In particular the statement that autoimmune hepatitis type 2 is associated with HCV infection and that cytochrome P450 2A6 is a significant autoantigen in hepatitis C is not widely accepted.

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Reply:

Dr. Michael Manns raises important questions regarding the role of molecular mimicry in the pathogenesis of chronic hepatitis C, as we discussed in HEPATOLOGY[1] and reported in *Journal of Experimental Medicine*.[2] Molecular mimicry could either lead to viral escape (the virus looks like self and is thus not recognized) or to postinfectious autoimmunity (the virus triggers an antiviral response which turns against self antigens). The presence or absence of tolerance to self decides which of the two outcomes prevails.

We recently reported that peripheral $CD8^+$ T cells from most HLA A2–positive individuals can be triggered by HCV core (aa 178-187) to recognize and kill cells presenting peptides derived from cytochrome P450 2A6 and 2A7 (aa 8-17) or endogenous cytochrome P450 2A6.[2] Both isoforms of cytochrome P450 were by themselves unable to induce an autoimmune response: the HCV-derived stimulus was required to trigger the cellular autoimmune response. This fits the observation that HCV infection can be associated and in some cases precedes the development of autoimmune hepatitis (AIH) type 2 (discussion and references in Kammer et al.[2]). Despite the fact that only a small proportion of chronic hepatitis C patients develop LKM-1 antibodies, the higher prevalence of HCV markers among patients with AIH type 2 compared with the normal population indicates an association between HCV and AIH type 2, at least in some cases.

Surface expression of cytochrome P450 2D6 on hepatocytes is still controversial. If P450 2D6 is not expressed at the cell surface, antibodies recognizing the intracellular form of the protein are not likely to be the cause of tissue injury but rather its consequence by mechanisms such as epitope spreading. A classic example is the case of postmyocardial/