CORRESPONDENCE

Incidence and Risk Factors of Hepatocellular Carcinoma in Patients With Primary Biliary Cirrhosis

To the Editor:

We read with great interest the article by Cavazza et al.,[1] who demonstrated that an advanced histological stage was the only risk factor associated with the development of hepatocellular carcinoma (HCC) in patients with primary biliary cirrhosis (PBC) from two European centers. Similar results were described in a Japanese multicenter study by Shibuya et al.[2] Although these studies suggest screening for HCC in patients with advanced-stage PBC, it is still uncertain whether there is a significantly increased risk of HCC development in patients with stage IV PBC cirrhosis versus patients with cirrhosis of other etiologies. We assessed in a single-center study the incidence of HCC in North American patients with stage IV PBC or autoimmune hepatitis (AIH) cirrhosis and compared it to the incidence of HCC in patients with hepatitis C virus (HCV) cirrhosis.

Three hundred fifteen patients with HCV cirrhosis, 49 patients with AIH cirrhosis, and 52 patients with stage IV PBC were evaluated at the Cleveland Clinic between 2001 and 2007. Stage IV PBC cirrhosis was diagnosed when patients had positive serological and histological findings of cirrhosis or biochemical and radiological evidence of portal hypertension. Cirrhosis due to AIH was defined by positive serological and histological findings of cirrhosis or biochemical and radiological evidence of portal hypertension. HCC-free survival was analyzed from the moment of the diagnosis of cirrhosis in HCV, AIH, and PBC patients until death or transplantation.

During a median follow-up of 3.6 years (with 25th and 75th percentiles of 1.8 and 6.3, respectively), 64 of 315 patients (20.3%) with HCV cirrhosis, 2 of 49 patients (4.1%) with AIH cirrhosis, and 4 of 52 patients (7.7%) with PBC cirrhosis developed HCC. The annual cumulative incidence of HCC was 1.1% in patients with AIH cirrhosis, 1.5% in patients with PBC cirrhosis, and 4.0% in patients with HCV cirrhosis (Fig. 1).

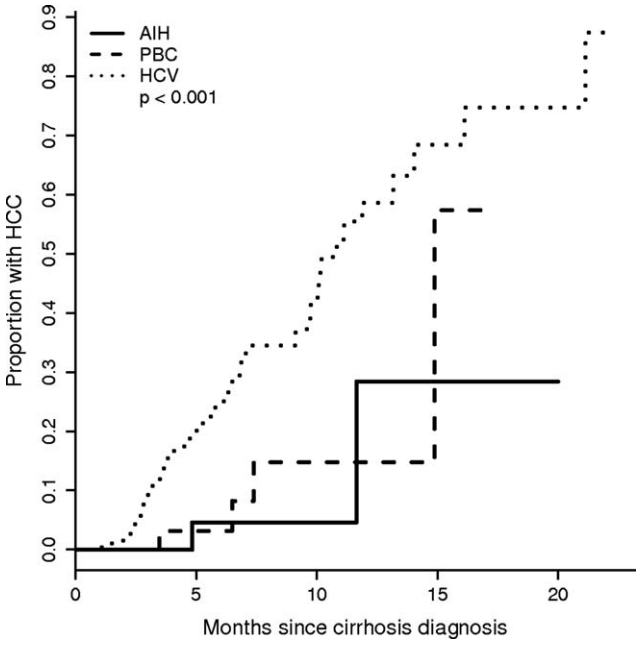

Fig. 1. Incidence of HCC in patients with AIH, PBC, or HCV.

This study has shown that although patients with stage IV PBC cirrhosis develop liver cancer, the risk is significantly lower in comparison with the risk for patients with HCV cirrhosis. The results of our study are discordant with a previously reported Spanish series in which the risks of HCC were similar in patients with late-stage PBC and in patients with HCV cirrhosis.[3] We agree with Cavazza et al.[1] that the low prevalence of PBC and the possible influence of geography on disease progression are confounding factors that may explain the divergent results in the literature. Future multicenter studies in North America with a longer follow-up period are necessary to validate these findings and better estimate the risk of HCC in PBC patients at an advanced histological stage.

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Reply:

We really appreciate the comments by Macaron et al. Indeed, the information that they have provided confirms the reported results indicating that the incidence of hepatocellular carcinoma (HCC) in patients with stage IV primary biliary cirrhosis (PBC) is approximately 1.5 to 1.8 cases per 100 person-years.[1,2] The commentary on the differences in the incidence of HCC in patients with advanced PBC and in patients with hepatitis C virus (HCV)–related cirrhosis should, however, be considered cautiously, particularly because some bias may have been incorporated into Macaron et al.'s analysis on account of factors such as the shorter period of follow-up (median = 3.6 years) and the lack of accurate information on the clinical characteristics and duration of cirrhosis in HCV-infected patients. Thus, the reported incidence of HCC in these latter patients with HCV cirrhosis is approximately 20% within a median of 3.6 years, whereas in most series assessed for longer periods, the incidence of HCC in patients with compensated HCV cirrhosis ranges from 4% to 7%.[2,3] In the recently published Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis study, the 5-year incidence of HCC was 7% for patients

with cirrhosis.[4] Among other factors, the shorter follow-up period in Macaron et al.'s analysis may explain the alleged differences between the two studies. Thus, in our study with a mean follow-up of 6.2 years, the cumulative incidence of HCC in patients with advanced PBC during the first 7 years was very low, but it then became similar to the incidence of HCC in an age-matched and sex-matched group of patients with HCV cirrhosis.[2] A comparable trend was observed in Macaron et al.'s analysis, but there was only 15 months of follow-up (see Figure in Macaron et al.'s letter). Likewise, we would like to make a comment on the potential influence of treatments delaying the progression and severity of liver damage, such as antiviral therapy in patients with HCV-related cirrhosis and ursodeoxycholic acid in patients with PBC. Certainly, in a cohort of 389 patients with PBC followed for an average of 9.5 years, the probability of HCC development was significantly reduced for those patients receiving ursodeoxycholic acid therapy.[5]

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Proceed With Caution: Peginterferon Alpha-2a Versus Peginterferon Alfa-2b in Chronic Hepatitis C. A Systematic Review of Randomized Trials

To the Editor:

Recently, Awad et al.[1] presented a meta-analysis comparing peginterferon alfa-2a and peginterferon alfa-2b for the treatment of hepatitis C virus (HCV) infection. The authors conclude: "Current evidence suggests that peginterferon alpha-2a is significantly superior to peginterferon alfa-2b regarding benefits (SVR, which is clearance of the virus from the blood)". After a careful revision of the article by Awad et al. and the original articles included in the meta-analysis, the conclusion they reach must be interpreted with caution. A main principle of meta-analysis deals with the homogeneity of the trials that will be analyzed together, in both aspects: population under study and methodological issues.[2,3] In addition, the quality of individual trials is important. However, these principles are not completely satisfied in the work of Awad et al.:

1. Two of the studies cited in Awad et al. (Sinha et al.[4] and Kolakowska et al.[5]) were published as abstracts, without peer review.

2. Three of the articles used a stratified randomization. Two of them (Ascione et al.[6] and Rumi et al.[7]) used a stratified randomization by genotype, and in the study by McHutchison et al.[8], randomization was stratified by level of HCV and race.

3. Whereas most of the trials included treatment-naive patients, Laguno et al.[9] worked with patients coinfected with human immunodeficiency virus and Scotto et al.[10] included patients without response to previous treatment.

4. McHutchison included different races, and although five trials included patients infected with genotype 1 to 4, two trials included patients with genotype 1 (McHutchison et al.[8] and Yenice et al.[11]), and Kolakowska et al. included only patients with genotype 3.

5. In the meta-analysis, 1016 patients with a lower dose of peginterferon alpha-2b were included.

Simultaneously, Alavian et al.[12] presented a very similar article: "The Comparative Efficacy and Safety of Peginterferon Alpha-2a vs. 2b for the Treatment of Chronic HCV Infection: A Meta-Analysis." Alavian et al. analyzed only five of the eight trials used by Awad et al. Alavian et al. reach nearly the same conclusion, but at the same time stated "A longer duration of maximum serum concentration compared with PEG-IFN-α2b (168 versus 48-72 hours) yields greater SVR and higher neutropenia in PEG-IFN-α2a recipients." Both authors[1,12] mentioned some awareness about the quality of the meta-analysis and the studies included in it. We think that conclusion must be interpreted both in light of the included trials and considering the effects of other factors, such as baseline HCV level, sex, race, and genotype. We strongly believe more research is needed before it is concluded one peginterferon is better than the other.

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Reply:

We thank Kershenobich and colleagues for their comments and the opportunity to explain our findings.[1] Overall, peginterferon alfa-2a significantly increased the number of patients who achieved sustained virological response in comparison with peginterferon alfa-2b [47% versus 41%, relative risk (RR) = 1.11, 95% confidence interval (CI) = 1.04-1.19, $P = 0.004$ (eight trials)]. Even with the lack of heterogeneity ($I^2 = 0\%$), we performed several sensitivity analyses to ensure the robustness of the results of our systematic review. A sensitivity analysis in which we included only trials with adequate randomization and allocation concealment did not noticeably change the estimated treated difference (RR = 1.12, 95% CI = 1.04-1.20). Similarly, the exclusion of the trial including patients with human immunodeficiency virus (RR = 1.12, 95% CI = 1.04-1.19), the trial with nonresponder patients (RR = 1.11, 95% CI = 1.04-1.19), and the two trials published only as abstracts (RR = 1.13, 95% CI = 1.04-1.22) did not noticeably change the estimated treatment difference. Excluding the low-dose peginterferon alfa-2b–treated patients from the Individualized Dosing Efficacy Versus Flat Dosing to Assess Optimal Pegylated Interferon Therapy trial, we again obtained an RR of 1.10 (95% CI = 1.03-1.19). A subgroup analysis by genotype was performed in our original study. Both subgroups (genotypes 1 and 4 and genotypes 2 and 3) yielded point estimates in favor of peginterferon alfa-2a and were not found to be statistically significantly different.

Kershenobich and colleagues question whether the use of stratified randomization in three of the included trials could have added to the heterogeneity across trials and thus reduced the validity of the overall estimate. Stratified randomization and conventional randomization are equally likely to achieve a prognostic balance between the considered intervention groups. The difference lies in the propensity to achieve a prognostic balance within subgroups (strata). Stratified randomization is better for achieving balance in prognostic factors within predefined strata. However, stratified randomization comes with the risk of creating prognostic imbalance within strata that are not used in the randomization if the sample size is small or the number of randomization strata is large. In the context of meta-analysis, stratified randomization, therefore, has the potential to either improve or jeopardize the validity of subgroup meta-analyses, but it is unlikely to affect the heterogeneity across trials. In our systematic review, we performed subgroup analyses by genotype. The trials by Ascione and Rumi were stratified by genotype. McHutchinson stratified by the hepatitis C virus level and race but included only genotype 1 patients. It is therefore likely that the stratified randomization used in the first two trials improved the validity of our subgroup analyses, whereas the stratified randomization used in the latter trial had no effect on the subgroup analysis.

Therefore, points I to V raised by Kershenobich and colleagues do not seem to have any devastating effect on the interpretation of our results. The aforementioned sensitivity analyses and theoretical considerations suggest that the included trials are sufficiently homogeneous to justify meta-analyses. On this basis, it should also be clear that overall peginterferon alfa-2a is superior to peginterferon alfa-2b in achieving a sustained virological response.

We agree with Kershenobich and colleagues that there may be a need for further trials. Such trials should be, as always, based on updated systematic reviews of the interventions at hand. Only in this way can we avoid redundant research within the field of hepatology.[2,3]

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Liver Enzymes and Cardiovascular Outcomes: a New Research Agenda

To the Editor:

We read with great interest the excellent article by Ghouri and coworkers,[1] who reviewed the current literature on the levels of gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT) as potential predictors of incident cardiovascular disease. The authors elegantly demonstrate that there may be a statistically significant association between higher GGT levels and incident cardiovascular disease events, although this association may be clinically questionable because it is confounded by age. In contrast, ALT levels are not significantly associated with cardiovascular risk. Based on these findings, the authors question the potential usefulness of cardiovascular risk screening based on the presence of nonalcoholic fatty liver disease (NAFLD). The authors are to be congratulated for their straightforward, clear, and concise presentation of the available material on this highly debated topic. One important issue raised by Ghouri et al.[1] is the observation that even when statistical adjustments have been made in previous studies, they have frequently been limited by weak variables such as the metabolic syndrome. Despite the overwhelming attention given to the metabolic syndrome in recent years, evidence is finally emerging that the diagnosis of this entity is an artificial construct that is less informative than the sum of its parts.[2,3] Of much interest and importance, no common pathophysiology has been elucidated as basis for the risk factors included in the definition of the metabolic syndrome.[4,5] We therefore endorse the authors' conclusion that an important point for future research in the field of liver enzymes as predictors of cardiovascular outcomes should consider all traditional vascular risk factors as potential confounders.[1] In light of the limited evidence of an association between liver enzymes and cardiac outcomes, further research is needed to shed more light on this issue. To fully achieve this goal, we should pay attention to the following issues in future research:

1. Even after adjustment for known risk factors, associations of GGT with cardiovascular events appear stronger in males than in females.[6] Therefore, sex-based subgroup analysis is necessary to clarify whether there are sex-related effects or relative risks.

2. It is necessary to clarify whether the association with cardiovascular events of elevated GGT differs between initially healthy individuals compared with patients with ultrasound-diagnosed NAFLD. This would help to disentangle the impact of the NAFLD diagnosis per se on cardiac outcomes. Indeed, NAFLD with normal liver enzymes is currently a widely accepted entity.[7]

3. Besides classical liver enzymes (GGT and ALT), it will be helpful to assess more sensitive biochemical markers of NAFLD, such as cytokeratin-18 fragments,[8] in relation to cardiovascular outcomes. This is an important issue inasmuch as ALT is not only a marker of NAFLD but also of ectopic fat in general.[9]

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Hepatitis C Trials That Combine Investigational Agents with Pegylated Interferon Should Be Stratified by Interleukin-28B Genotype

To the Editor:

We read with interest the recent article by Akuta and colleagues,[1] who reported the association between interleukin-28B (*IL-28B*) polymorphism and the treatment response in a cohort of Japanese patients treated with telaprevir and pegylated interferon-alfa (peg-IFN)/ribavirin (RBV) combination therapy. The good-response genotype (C/C rs12979860 or T/T rs8099917) was strongly associated with an increased rate of sustained virological response despite the addition of a directly acting antiviral agent. This suggests that patient *IL-28B* genotype will remain relevant in the dawning era of specifically targeted antiviral therapy for hepatitis C virus because a combination with peg-IFN and RBV is required to restrict the development of antiviral resistance. It will, therefore, be important to consider *IL-28B* genotype in clinical development programs; because of the population frequency of the good-response *IL-28B* variant and its association with rapid viral decline during peg-IFN therapy,[2] it is possible for small early-phase efficacy trials to be confounded by an imbalance in the *IL-28B* genotype across treatment arms.

We statistically modeled the probability of an imbalance in the good-response *IL-28B* variant (C/C rs12979860) between treatment arms for three hypothetical situations: a phase 1 trial (n = 60), a phase 2a trial (n = 120), and a phase 2b trial (n = 240). Each involved three randomized arms (Fig. 1). The probability of an imbalance in one treatment arm of ±10% (<23% or >43% when the C/C genotype frequency was assumed to be 33%[2]) was 31%, 18%, and 6% for the phase 1, 2a, and 2b trials, respectively, and the probability of an imbalance in one treatment arm of ±20% was 10%, 0.4%, and <0.01% for the phase 1, 2a, and 2b trials, respectively. We assumed a Caucasian population for this analysis; the inclusion of other ethnic groups would be expected to increase the risk of sampling error.[2]

We then modeled the implications of such an imbalance for the primary outcome of viral load reduction at week 4 in studies combining a direct antiviral agent with peg-IFN and RBV (Table 1). An imbalance in the *IL-28B* genotype of 10% to 20% could lead to differences in HCVRNA reduction of 0.2- to 0.5-$\log_{10}$ IU/mL between treatment arms due to peg-IFN alone. This has great relevance for dose-finding studies in which the dose-related antiviral potency must be weighed against toxicity. In the setting of more extreme mismatching (e.g., in a mixed-ethnicity cohort), confounding by *IL-28B* genotype might even affect the decision to advance a compound from proof of concept to the next stage of clinical development. Indeed, Anadys Pharmaceuticals recently reported an imbalance in the frequency of the C/C genotype that confounded the week 12 results of a phase 2 trial (the C/C genotype frequency was 21% in the active treatment arms and 56% in the control arm).[3]

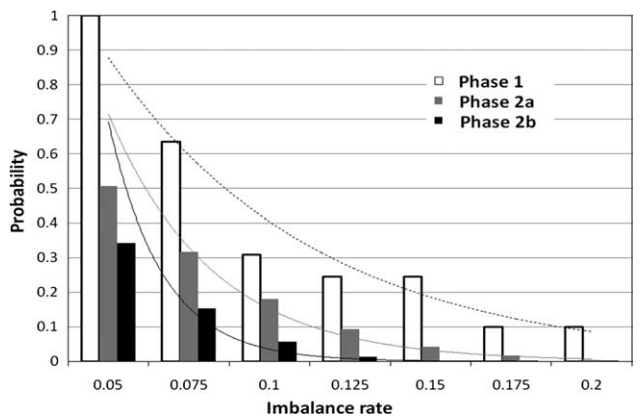

Fig. 1. Probability of an imbalance in the IL-28B genotype frequency in one arm of an early-phase clinical trial involving three randomized treatment arms. The columns represent the probability of an imbalance at the specified levels; the curves represent the continuous probability distribution. The phase 1 study was assumed to involve 60 patients (20 per treatment arm), the phase 2a study was assumed to involve 120 patients, and the phase 2b study was assumed to involve 240 patients.

Table 1. Apparent Differences in the Antiviral Efficacy Resulting from an Imbalance in the *IL-28B* Genotype Frequency Between Treatment Arms in Early-Phase Trials

Imbalance Between Treatment Arms	Arm A: Placebo and Peg-IFN/RBV (n = 20)	Arm B: Antiviral (Dose 1) and Peg-IFN/RBV (n = 20)	Arm C: Antiviral (Dose 2) and Peg-IFN/RBV (n = 20)
10%			
C/C *IL-28B* type (%)	23	33	43
Non-C/C *IL-28B* type (%)	77	67	57
Mean viral load reduction at 4 weeks ($\log_{10}$ IU/mL)	2.0	2.2	2.4
20%			
C/C *IL-28B* type (%)	13	33	53
Non-C/C *IL-28B* type (%)	87	67	47
Mean viral load reduction at 4 weeks ($\log_{10}$ IU/mL)	1.7	2.2	2.7

We assumed that (1) the candidate drug had no antiviral activity, (2) the frequency of the good-response (C/C) *IL-28B* type was 33%, (3) the viral load reduction with the good-response (C/C) *IL-28B* type at week 4 was 3.8-$\log_{10}$ IU/mL, and (4) the viral load reduction with the poor-response (non-C/C) *IL-28B* type at week 4 was 1.4-$\log_{10}$ IU/mL.[2]

IL-28B genotype distribution is therefore an important consideration when early-phase hepatitis C virus clinical trials are being undertaken and their results are being interpreted. In the research setting, the typing of the *IL-28B* polymorphism is a straightforward, inexpensive test. We believe that treatment arms should be stratified by the *IL-28B* genotype. This is particularly relevant to early studies of direct antivirals in combination with peg-IFN and RBV for which antiviral efficacy is the primary outcome.

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Potential conflict of interest: Alexander J. Thompson, Jacques Fellay, Dongliang Ge, David B. Goldstein, and John G. McHutchison are co-inventors of a patent related to the discovery of interleukin-28B.

Hypovitaminosis D and Ethnic Differences in Insulin Resistance

To the Editor:

I read with great interest the article by Guerrero et al.,[1] who used a large population-based study and several spectroscopic and imaging methodologies to assess the contribution of body fat distribution to the differing rates of hepatic steatosis in the three major US ethnic groups (African American, Hispanic, and Caucasian). They suggested that the differing rates of hepatic steatosis among the three ethnic groups are associated with similar differences in visceral adiposity. Interestingly, in comparison with either Hispanics or Caucasians, African Americans appear to be more resistant to the hypertriglyceridemia associated with insulin resistance despite their lower levels of intraperitoneal and liver fat.[1] Here I propose hypovitaminosis D as a potential underlying mechanism for the high prevalence of insulin resistance in African Americans on the basis of the following findings.

First, numerous studies have demonstrated that vitamin D insufficiency and hypovitaminosis D are more prevalent among African Americans than other Americans.[2-6] This is primarily due to the fact that pigmentation reduces vitamin D production in the skin.[2] A cross-sectional analysis of serum 25-hydroxyvitamin D levels showed that hypovitaminosis D was present in a substantial proportion of the studied African American population, even in the South and among those meeting recommended dietary guidelines.[5] Moreover, no significant difference was found in the proportion of vitamin D insufficiency between obese and nonobese preadolescent African American children.[6]

Second, previous studies have established that vitamin D insufficiency and hypovitaminosis D are associated with insulin resistance.[7-9] For instance, by using a hyperglycemic clamp technique in a group of healthy, glucose-tolerant subjects, Chiu et al.[9] showed a positive correlation between the 25-hydroxyvitamin D concentration and insulin sensitivity, and subjects with hypovitaminosis D were found to be at higher risk for insulin resistance and metabolic syndrome.

These findings make it rational for us to infer that the prevalence of vitamin D insufficiency and hypovitaminosis D among African Americans can increase their risk of insulin resistance. This may account in part for the fact that despite the lower levels of intraperitoneal and liver fat in African Americans, their prevalence of insulin resistance is similar to that of Hispanics, who possess the highest intraperitoneal and liver fat levels.[1] Therefore, vitamin D insufficiency and hypovitaminosis D in African Americans may provide useful clues for understanding their high prevalence of insulin resistance.

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Drug-Induced Postinfantile Giant Cell Hepatitis

To the Editor:

We have read with great interest the article by Björnsson et al.[1] on the topic of drug-induced autoimmune hepatitis (AIH). The authors concluded that a significant proportion of patients with AIH have drug-induced AIH. Together with different types of drugs, medicinal herbs and cosmetics may be involved in liver damage.[2] Postinfantile giant cell hepatitis (PGCH) is a rare entity secondary to a nonspecific reaction to toxins, drugs, or viruses, although no causative agent has been found in many cases.[3,4] Importantly, several patients have exhibited autoimmune characteristics and have responded to immunosuppressive therapy.[5,6] The clinical spectrum of PGCH is variable; according to some authors,[3,7] the disease in its natural course is usually fulminant and within months progresses to cirrhosis, which will lead to death or a requirement for liver transplantation. However, a benign course in these patients can also be observed. Here we discuss a 38-year-old woman who, having PGCH and features of AIH associated with a drug used to prevent hair loss, responded to corticosteroids plus azathioprine.

The patient, presenting progressive jaundice (total bilirubin level = 28.7 mg/dL) without pain during the previous 3 weeks, was admitted to our hospital. The laboratory investigation revealed elevated serum levels of aspartate aminotransferase (714 IU/L), alanine aminotransferase (465 IU/L), gamma-glutamyltransferase (98 IU/L), and alkaline phosphatase (268 IU/L), and she was positive for antinuclear antibody (titer = 1/160) with normal immunoglobulins. The only relevant previous history was her treatment for more than 10 months with Pil-Food (Laboratorio Serra Pamies, Reus, Spain) to prevent hair loss. An ultrasonography examination found only regular hepatomegaly, and percutaneous liver biopsy was performed. A histological study (Fig. 1) showed not only a conserved architectural structure but also extensive areas of multinucleate giant cells, portal tract enlargement with bridging necrosis, intense inflammation of the parenchyma, and liver cell necrosis with regenerative changes and hyperplasia of the mononuclear phagocytic system. Furthermore, marked intracanalicular and hepatocellular cholestasis was observed. When she was admitted to the hospital, the Pil-Food therapy was stopped, and treatment with ursodeoxycholic acid (14 mg/kg/day) was initiated; substantial analytical changes were not attained. Because of the probable AIH component, a course of methylprednisolone (60 mg/day) was started, and the dose was subsequently tapered until total remission was achieved. As a unique maintenance therapy, azathioprine (50 mg/day initially and 25 mg/day after the first year) was used. In month 12 after the diagnosis and treatment, the biochemical investigation was completely normal (aspartate aminotransferase level = 14 IU/L, alanine aminotransferase level = 12 IU/L, total bilirubin level = 0.5 mg/dL, alkaline phosphatase level = 62 IU/L, and gamma-glutamyltransferase level = 12 IU/L); her antinuclear antibody positivity persisted (titer = 1/80). After more than 5 years of follow-up, the patient's liver test findings continued to be normal, and she remained asymptomatic.

The cause of PGCH is unknown and probably multifactorial; possibilities include a virus,[8,9] drugs and herbal remedies,[10] and autoimmune changes.[11,12] In addition, reports have been published about patients who have undergone liver transplantation.[13,14] Our patient received Pil-Food. Severe changes in liver function tests occurred, she was positive for antinuclear antibody autoreactivity, and a histological examination found abundant areas of multinucleate giant cells with marked periportal and parenchymal hepatocellular necrosis and inflammation. Because all the aforementioned alterations appeared during the long-term ingestion of Pil-Food [a composition developed by Synthelabo that contains D,L-methionine, L-(+)-cysteine hydrochloride, L-cysteine, enzymes and animal protein hydrolysates, millet extract, calcium pantothenate, vitamin B2 phosphate, vitamin B6, biotin (vitamin H), and vitamin E] and a successful corticosteroid response was attained, we speculate that this hepatic autoreactivity could be related to the Pil-Food treatment.[15,16] Moreover, just like patients with drug-induced AIH,[1] our patient did not require long-term immunosuppressive therapy. We believe that this case highlights (1) that the breakdown of immune tolerance by drugs is able to trigger liver autoreactivity and (2) that some cases of PGCH may present a rapid and effective response to corticosteroid therapy instead of a fulminant or progressive course.

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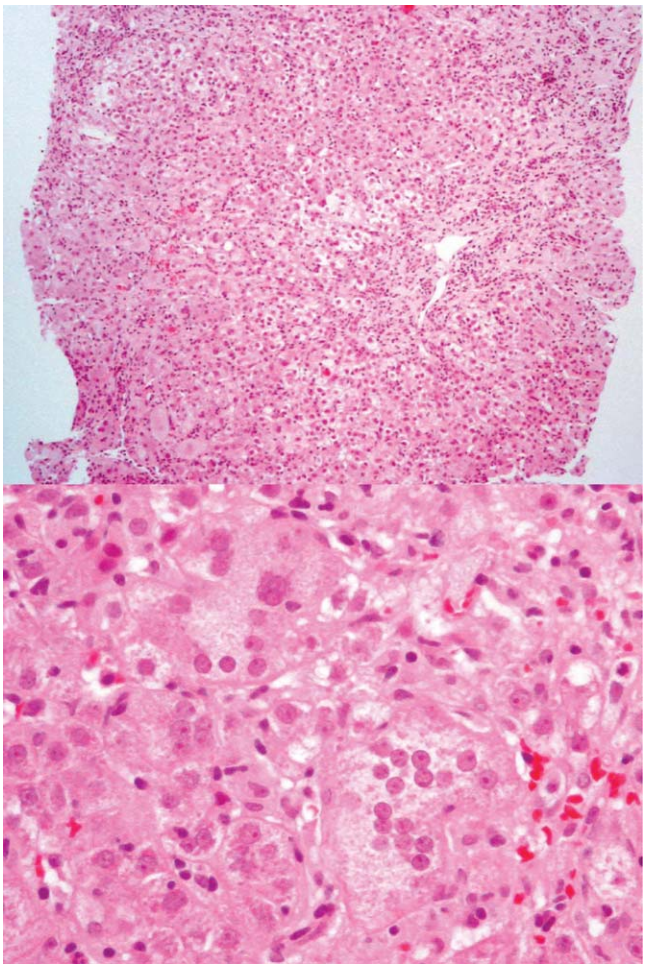

Fig. 1. Conserved architectural structure with extensive areas of multinuclear giant cells, portal tract enlargement with bridging necrosis, inflammation, regenerative changes and mononuclear cells hyperplasia.

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Drug-Induced Autoimmune Hepatitis Caused by Anti–Tumor Necrosis Factor α Agents

To the Editor:

We read with great interest the report by Björnsson et al.[1] regarding the clinical characteristics and prognosis of patients with drug-induced autoimmune hepatitis (DIAIH). In their study, the authors described 24 patients with DIAIH resulting from nitrofurantoin and minocycline use.

Tumor necrosis factor α (TNF-α) blocking agents are drugs commonly used in the treatment of rheumatological, dermatological, and gastroenterological autoimmune diseases. Minor abnormalities in liver function tests are relatively common with the use of anti–TNF-α agents, but the development of serious hepatic failure and the reactivation of viral hepatitis might be possible as well. Autoimmune hepatitis (AIH) is a rare but increasingly reported complication with the use of anti–TNF-α agents. To the best of our knowledge, 11 cases of AIH due to anti–TNF-α agents were reported between 2001 and 2010, and all these patients showed serological findings of type 1 AIH.[2–12] The induction of ANA and the elevation of serum immunoglobulin G levels, which are diagnostic criteria for AIH, have been reported in patients treated with anti–TNF-α therapy for spondylarthropathy, rheumatoid arthritis, and psoriasis.[13,14] For these reasons, reliance on only serological and laboratory findings may lead to diagnostic confusion. Moreover, after a careful review of the literature, we noticed that none of the patients with AIH induced by anti–TNF-α agents had histologically proven cirrhosis or advanced fibrosis at presentation, and all of them responded well to immunosuppressive treatment. Therefore, these findings suggest that the prognosis of DIAIH is favorable, regardless of the underlying, offending drugs.

In conclusion, DIAIH is a rare entity, and only a few drugs have been reported as offending agents. We think that anti–TNF-α agents, in addition to well-known drugs, should be considered noxious agents in the differential diagnosis of DIAIH. Moreover, anti–TNF-α agents share some similarities with nitrofurantoin and minocycline with respect to AIH. All these drugs show the same histological findings, and their clinical characteristics with respect to therapeutic outcomes are nearly identical. However, anti–TNF-α agents have many hepatic side effects such as drug-induced hepatitis, reactivation of hepatitis B or C, and fulminant hepatic failure, which may require orthotopic liver transplantation. Therefore, we think that liver enzyme abnormalities should be carefully evaluated in patients who are receiving anti–TNF-α agent therapy. After the exclusion of other possible side effects of anti–TNF-α agents, biopsy findings specific to AIH and a good response to immunosuppressive therapy are essential parts of the diagnosis of AIH induced by anti–TNF-α agents.

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Treatment Response in Patients with Autoimmune Hepatitis

To the Editor:

We congratulate Manns and colleagues[1] on their comprehensive review of and guidelines for the treatment of autoimmune hepatitis (AIH). The importance of complete biochemical remission, which is defined as normalization of aminotransferases and immunoglobulin G (IgG)/gamma-globulins, is underlined as the ideal treatment endpoint and as the goal of initial therapy. Notably, normalization of only aminotransferases is still being used as a definition of biochemical remission.[2] We and others have previously shown that elevated levels of aminotransferases, IgG/gamma-globulins, or both may indicate histological activity, and this in turn indicates an increased risk of disease relapse and progression.[3,4] Therefore, complete biochemical remission as a surrogate parameter for histological remission should be achieved with as few side effects as possible. In addition, recent studies have suggested that a fast response to treatment may be associated with a better outcome.[5,6]

With the two treatment algorithms proposed in the guidelines, adults rarely achieve resolution of their laboratory and liver tissue abnormalities in less than 12 months, and a complete response rate of only 11% has been reported with 6 months of treatment.[6] This is supported by the recent and so far largest controlled treatment trial for AIH, which compared prednisone (40 mg daily) as the initial therapy to budesonide, each in combination with azathioprine.[2] Here, prednisone was able to induce biochemical remission (defined as normalization of aminotransferases) with 6 months of treatment in only 39% of patients. Patients with cirrhosis were excluded from this trial. We are concerned by this rather low biochemical response rate, which may be associated with a poorer outcome,[5,6] and we are also worried that a prednisone maintenance dose of 20 mg or less until remission, as stated in the guidelines, is associated with considerable long-term steroid side effects.

We therefore suggest a more individualized treatment regimen that has been reported to result in excellent long-term prognosis.[7] This approach includes an initial dose of prednisolone of 1 mg/kg of body weight, which is rapidly tapered within the next 3 months to a maintenance dose of 5 to 10 mg/day. This treatment is combined from the beginning with azathioprine at a dose of 1 to 1.5 mg/kg of body weight, unless severe hyperbilirubinemia is present. We have reviewed our current experience and report data from 92 patients with AIH for whom complete laboratory follow-up data at months 0, 1, 3, and 6 are available (Fig. 1). Patients with cirrhosis were excluded from this analysis in order to allow a better comparison with the recently published treatment trial.[2] With this approach, a reduction of both aminotransferases and IgG/gamma-globulins to less than 2 times the upper limit of normal within 6 months of treatment was not reached by only 10% of the patients. Normalization of aminotransferases was achieved in 77%, and normalization of both aminotransferases and IgG/gamma-globulins was achieved in 64% at 6 months. At our center, patients with a complete biochemical response are taken off prednisolone after 1 year of treatment, and they are maintained on azathioprine until histological remission occurs.

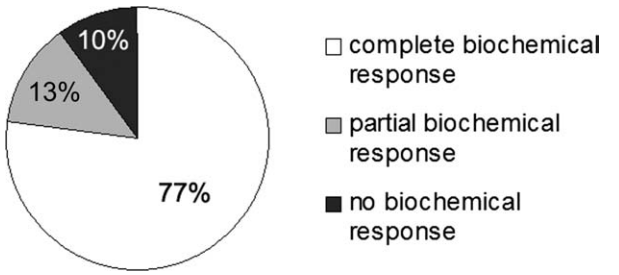

Fig. 1. Biochemical response after 6 months of treatment in 92 patients with noncirrhotic AIH. Complete response is defined as normalization of aminotransferases and IgG/gamma-globulins, partial response is defined as a reduction of aminotransferases and IgG/gamma-globulins to less than 2 times the upper limit of normal, and no response is defined as none of the above.

Because of the high and fast response rates, we strongly believe that this regimen spares patients long-term steroid exposure, reduces long-term side effects, and helps to achieve histological remission and therefore should improve the prognosis of our patients. The liver transplantation–free survival rate in this cohort of patients was 100% after a mean observation time of 60 months.

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Nonalcoholic Fatty Liver in a Developing Country is Responsible for Significant Liver Disease

To the Editor:

We read with great interest the article by Das et al.[1] published in a recent issue of HEPATOLOGY. We agree with the authors that there is a significant prevalence of nonalcoholic fatty liver (NAFL) in the nonobese population and potentially significant liver disease related to NAFL in India. Even though our data were hospital-based, we suggested earlier that Indians with nonalcoholic fatty liver disease (NAFLD) do not suffer from the morbid overweight and obesity seen in the West but do have a metabolic profile (including insulin resistance) similar to that of their Western counterparts.[2,3] Even though the mean body mass index (BMI) was only 28.7 kg/m^2, the majority of our patients suffered from overweight (21%), obesity (68%), or central obesity (82%) according to the Asia-Pacific guidelines.[3] Although Das et al. used Asia-Pacific cutoffs for central obesity, their figures for overweight and obesity would have been higher (by at least 48%) even in the community population if they had used the Asia-Pacific cutoffs for defining overweight (BMI >23 but <25 kg/m^2) and obesity (BMI ≥ 25 kg/m^2).[4,5] Lower BMI cutoffs have been suggested for Asian populations because of the findings of higher percentages of body and visceral fat at a given BMI and higher morbidity and mortality rates at lower BMIs in Asians versus other populations.[6,7]

Das et al.[1] looked only at serum ferritin levels in their patients and found these to be normal; we studied in detail the serum (serum iron, transferrin saturation, serum ferritin, and total iron binding capacity), hepatic iron overload (Perls' Prussian blue staining), and hemochromatosis gene mutations and did not find these to be abnormal in Indian patients with NAFLD.[8,9] Similarly to Das et al., we also observed mild histological disease (a mild/moderate grade of inflammation with no or mild/moderate fibrosis) in patients with NAFLD presenting with elevated aminotransferase levels.[2,3] Only 51% of our patients (22 of 43) had histological nonalcoholic steatohepatitis (NASH), and none had cirrhosis at presentation,[3] whereas for Das et al., 31% of the patients had NASH, and 2.4% of the patients (4) had cirrhosis due to NAFL.

Despite mild histological disease at presentation, patients with histological NASH have a propensity to progress to cirrhosis and hepatocellular carcinoma (HCC) and at that stage may be identified only by the presence of surrogate markers of NAFLD.[10] We recently studied surrogate markers of NAFLD in 65 patients with cryptogenic cirrhosis and in 39 patients with cryptogenic hepatocellular carcinoma (CHCC) and compared the results to those for 50 patients with virus-related cirrhosis (VCC) and 39 patients with virus-related hepatocellular carcinoma (VHCC) of comparable age, gender, and liver disease severity. The study was approved by the institute's ethical review committee, and all patients provided informed consent. The diagnosis of cirrhosis was based on clinical findings, biochemistry, imaging, the demonstration of varices on gastroscopy, and histology (when available), and the presence of HCC was based on the practice guidelines of the American Association for the Study of Liver Diseases.[11] All possible etiologies for cirrhosis and HCC, including viral etiologies, autoimmune etiologies, Wilson's disease, and iron overload, were excluded. Screening for occult hepatitis B virus infection (by total antibodies against core antigen) and celiac disease (by anti-tissue transglutaminase antibodies, anti-endomysial antibodies, and duodenal biopsy) was also performed in 16 and 10 patients, respectively. Abnormal metabolic parameters and metabolic syndrome were defined according to Adult Treatment Panel III criteria[12] with a modified waist circumference for the Asia-Pacific region.[5] The mean BMI was higher in patients with cryptogenic cirrhosis (26.06 ± 5.96 kg/m^2) versus patients with VCC (22.12 ± 1.71 kg/m^2, $P = 0.0001$). A higher number of patients with cryptogenic cirrhosis had an abnormal waist circumference [38 (58.5%) versus 15 (30%), $P = 0.004$], type 2 diabetes mellitus [26 (40%) versus 5 (10%), $P = 0.0007$], and lower serum high-density lipoprotein levels [35 (53.8%) versus 3 (6%), $P = 0.0003$] in comparison with patients with VCC. Patients with CHCC had a higher BMI (24.35 ± 4 versus 22.5 ± 3.4 kg/m^2, $P = 0.03$) and a higher prevalence of type 2 diabetes mellitus [15 (38.5%) versus 7 (17.9%), $P = 0.04$] in comparison with patients with VHCC. There was no difference in abnormal high-density lipoprotein, serum triglycerides, or hypertension between patients with CHCC and patients with VHCC. The prevalence of metabolic syndrome was also similar in the two groups of patients with cirrhosis and HCC.

In conclusion, the higher prevalence of metabolic risk factors, if they are taken as surrogate markers of NAFL, suggests that NAFL is an important cause of both cryptogenic cirrhosis and CHCC and thus contributes to significant liver disease in India.

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