

Peginterferon and Lamivudine for Hepatitis B

TO THE EDITOR: Marcellin and colleagues (Sept. 16 issue)¹ report that patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B had higher rates of a sustained response to treatment with peginterferon alfa-2a than with lamivudine.¹ HBeAg-negative chronic hepatitis B is usually associated with precore mutations,² but it may also develop in patients infected with wild-type strains, with mutations in the basic core promoter.³ Whether these two groups of patients with HBeAg-negative chronic hepatitis differ in their responses to therapy is not known. The study by Marcellin et al. would have been more informative if hepatitis B virus (HBV) genome sequencing and genotyping had been performed in all the patients.

Marcellin and colleagues also report that a more profound suppression of HBV DNA, as seen with combination therapy, led to a lower incidence of lamivudine resistance. We suggest an alternative explanation for this finding. Interferon may allow the immune response to clear infected hepatocytes by restoring T-cell reactivity more efficiently and more durably than lamivudine.⁴ Whether this CD4-mediated response to HBV antigens occurred concomitantly with a rapid decline of viremia has yet to be determined.

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1. Marcellin P, Lau GKK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004;351:1206-17.
2. Carman WF, Jacyna MR, Hadziyannis S, McGarvey M, Karayiannis P, Thomas HC. Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. *Lancet* 1989; 2:588-91.
3. Lindh M, Horal P, Dhillon AP, Furuta Y, Norkrans G. Hepatitis B virus carriers without precore mutations in hepatitis B e antigen-negative stage show more severe liver damage. *Hepatology* 1996; 24:494-501.
4. Boni C, Bertoletti A, Penna A, et al. Lamivudine treatment can restore T cell responsiveness in chronic hepatitis B. *J Clin Invest* 1998;102:968-75.

DR. MARCELLIN REPLIES: HBV genome sequencing and genotyping were performed in the majority of the patients in our study (>94 percent), and baseline data have been presented elsewhere.¹ Data on treatment responses stratified according to the presence or absence of mutations in the precore or basic core promoter cannot be discussed in detail in the context of this reply. However, univariate and multivariate analyses that included all treated patients showed that the presence or absence of such mutations was not significantly associated with a sustained response. Data on the effect of the HBV genotype are too complex to do justice to them in this reply, but some of our findings, including the potential benefit of combination therapy with peginterferon alfa-2a plus lamivudine in patients with genotype D, have recently been reported.²

The exact mechanism that leads to a reduced incidence of lamivudine resistance in the combination-therapy group is not known, although we discuss some of the theories in our report. Assy and Hussein's theory regarding the enhanced restoration of CD4-mediated responses with peginterferon alfa-2a is interesting. However, T-cell activity in response to peginterferon alfa-2a, with or without lamivudine, was not analyzed in our study.

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1. Marcellin P, Lau GKK, Bonino F, et al. A Phase III, partially double-blinded study evaluating the efficacy and safety of peginterferon alfa-2a (40KD) (PEGASYS) alone or in combination with lamivudine vs lamivudine in 546 patients with HBeAg-negative/anti-HBe-positive chronic hepatitis B. *Hepatology* 2003;38:Suppl 1:724A-725A. abstract.
2. Bonino F, Lau G, Marcellin P, et al. The first detailed analysis of predictors of response in HBeAg-negative chronic hepatitis B: data from a multicenter, randomized, partially double-blind study of peginterferon alfa-2a (40KD) (PEGASYS) alone or in combination with lamivudine vs lamivudine alone. *Hepatology* 2004;40:Suppl 1: 659A. abstract.

Public Access to Biomedical Research

TO THE EDITOR: The *Journal's* support (Sept. 23 issue)¹ for the proposal of the National Institutes of Health (NIH) to make the results of NIH-sponsored research more readily available to the public² is com-

mendable, as is its policy of making articles freely available six months after the publication date. However, the editorial by Drs. Drazen and Curfman makes misleading claims regarding copyright. The

editorialists say that the *Journal* “will continue to seek redress if others use what we publish for commercial purposes.” Authors would benefit most from the widest possible distribution of their work, commercial or noncommercial. They also suggest that copyright must be held by publishers in order to protect “intellectual integrity.” But whether or not copyright is transferred, authors retain the moral rights associated with an article, including the rights of integrity and of attribution.

Not owning copyright in no way prevents a publisher from taking legal action in the case of misuse or misrepresentation. Since both the publishers’ and the authors’ reputations are at stake, publishers should defend scientific integrity — which does not depend on ownership of copyright. Scientific integrity should not be used as a smokescreen by publishers to conceal their self-interest.

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Drs. Cockerill and Velterop report that they are both directors of BioMed Central.

1. Drazen JM, Curfman GD. Public access to biomedical research. *N Engl J Med* 2004;351:1343.
2. Enhanced public access to NIH research information. (Accessed December 1, 2004, at <http://grants.nih.gov/grants/notice-files/NOT-OD-04-064.html>.)

TO THE EDITOR: The discussion of copyright issues is predicated on a misunderstanding of the implications for intellectual property considerations of the policy proposed by the NIH. Many publishers currently deposit some or all of their journals’ content in PubMed Central, the full-text version of PubMed. When publishers do so, they do not relinquish copyright to the articles. In its “Supplemental Terms of Use for Proceedings of the National Academy of Sciences (PNAS),” for example, the National Academy of Sciences lists a number of binding stipulations for users accessing PNAS through PubMed Central.¹ These include the explicit requirement that any further reproduction of the journal (beyond standard terms of fair use) in any medium be accompanied by the written permission of the academy. In other words, it is simply not true that, as Drazen and Curfman state, “under the proposed rule, a commercial entity could republish [an article from the *Journal*], highlighting the benefits but ignoring the disadvantages, and attribute the work to the *Journal*.”

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1. Proceedings of the National Academy of Sciences of the United States of America. Supplemental Terms of Use for the Proceedings of the National Academy of Sciences (PNAS). (Accessed December 1, 2004, at <http://www.pnas.org/misc/nlmterms.shtml>.)

DRS. DRAZEN AND CURFMAN REPLY: We believe that publishers should retain copyright to articles, because it is central to protecting their integrity. It is not clear from the language of the NIH proposal that copyright would be maintained in the version of the work they propose to host, and certain participants in the debate, including the Public Library of Science, have proposed using Creative Commons’ protections, which would allow broad use, only by attribution and not granted permission, of research publications, including commercial republication with the potential for alterations.

One of our objectives in writing the editorial was to ensure that the issue of copyright was addressed. We believe it is important to be on the record with our views and experiences, and we have filed the editorial with the NIH as part of the public-commentary period on the proposed regulations concerning open access in the hope that the NIH will specifically address copyright protections. We do not assume that the copyright processes or rules of PubMed Central, to which Gass refers, would carry over to the NIH repository, because other elements of the current implementation of PubMed Central are incompatible with the NIH proposal.

We disagree with Cockerill and Velterop that publishers can effectively protect the integrity of published research without owning copyright — our experiences have shown us how aggressive and cavalier some infringers can be. Authors are typically not in a position to detect or prosecute copyright violations. More important, journals, along with authors, have a justifiable interest in protecting the intellectual integrity of published articles, since journals invest substantial editorial resources in ensuring the validity and accuracy of the research. Vigorous protection of copyright is clearly in the best interest of the medical community and of the patients it serves.

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