Trading Ivy for Palm Trees
9th Annual Princeton Workshop Meets in Hawaii

Since 1995, the Hepatitis B Foundation (HBF) has sponsored the annual Princeton Workshop to stimulate scientific dialogue about critical issues in the development of therapies for chronic hepatitis B. Every year the HBF invites 20 to 30 thought leaders in the field from academia, government and industry to gather for intense roundtable discussions.

Princeton, NJ, is certainly a good place for big thinking. However, when the offer came to host the Princeton Workshop in Hawaii every other year, there wasn't a lot of resistance. Everyone was happy to trade ivy-covered buildings for a tropical resort with exotic palm trees.

On December 16, 2003, the HBF's 9th annual Princeton Workshop was held as a special session for the second time at the HepDART conference in Kauai, Hawaii. The HBF sponsored session focused on surrogate markers used for evaluating the effectiveness of current and future hepatitis therapies.

The session began with an overview by **Joan Block**, **RN**, HBF co-founder and senior advisor, about the HBF's expanding outreach efforts and the wave of cooperation between nonprofit organizations and public health agencies to create national initiatives highlighting hepatitis B and C: the Liver Disease Research Branch at the National Institutes of Health, National Viral Hepatitis Roundtable, Center for Disease Control's National Task Force on Hepatitis B for Asian American and Pacific Islanders, and the American Liver Foundation's THINK Hepatitis B Campaign.

Scientific presentations about the proteomics of early disease detection and the surrogate markers used for evaluating the effectiveness of hepatitis treatments were given by a distinguished panel: **Timothy Block**, **PhD**, HBF president (Thomas Jefferson University); **W. Thomas London, MD**, HBF board member (Fox Chase Cancer Center); **Adrian DiBisceglie**, **MD**, St. Louis University of Health Sciences Center; and **Michael Fried**, **MD**, University of North Carolina, Chapel Hill.

Highlights Of The 9th Annual Princeton Workshop

The Princeton Workshop is typically structured around important questions. Participants lend their experience and expertise to the lively, interactive discussions. Although conclusions are not always possible, important new ways of looking at questions can help re-direct or re-focus the researchers and clinicians working together to find a cure for hepatitis B.

What is the best way to monitor viral hepatitis?

There was a lively discussion of how best to monitor people with viral hepatitis for signs of illness. This is of particular concern in evaluating the usefulness of new or experimental drugs and was the subject of last year's Princeton Workshop. Thus, this year's workshop session was an important follow-up with new information discussed.

Historically, the liver biopsy has been considered to be the "gold standard" of treatment. However, this is expensive, comes with some risks to the patient, and inconveniences the patient for at least an entire day. The question is, in light of new information discussed at this year's Workshop, is a liver biopsy still necessary, or can other "surrogates" or substitutes be used instead?

For hepatitis B, the two categories of diagnostic tests most often monitored are "liver function tests" and "virological markers". The *liver function tests* refer to the measurement of the amount of liver cell components that spill into the bloodstream when the liver is damaged. These include "AST" and "ALT" enzymes.

The *virological markers* are either components of the virus, such as viral DNA, core protein (HBc), e-antigen (eAg), surface antigen (sAg), or the antibodies our body makes in response to seeing these viral components - surface antibody (sAb), anti-eAg (anti-HBe), anti-core (anti-HBc).

Can early virological response be predictive of a beneficial outcome?
Early virological response refers to a rapid reduction in the amount of hepatitis B virus (HBV) or more specifically, the virological markers described above. Here is where hepatitis B and hepatitis C treatment responses may differ.

It appears that "early virological response" to interferon therapy in hepatitis C virus (HCV) patients is a good predictor of whether or not the interferon will be effective. Thus, decent reductions in the amount of HCV RNA (within a few weeks of starting interferon treatment), may forecast who will benefit from this treatment. This finding seems to make a prediction for many, but not all, so the usefulness of this information on an individual basis is not clear.

For HBV-infected individuals, the results appear to be different. Early virological response (within weeks of starting interferon therapy) does not appear to correlate very well with predicting who will benefit. Since most people treated with lamivudine or adefovir will have early virological responses of reduced HBV DNA in their blood, this is not a reliable predictor of long-term, sustained benefit.

Early virological response vs. Sustained virological response
Reductions in the amount of HBV DNA in the blood as a result of treatment correlated favorably to clinical outcomes (including biopsy information) in those with elevated ALTs at the beginning of treatment. The situation for eAg-negative patients was less striking. Nevertheless, a fairly consistent pattern was seen (as reported by Dr. London) in which sustained reductions of viral DNA from "baseline" (the amount of virus in a person immediately before treatment) by at least 10 fold are accompanied by reduced liver disease (as measured by biopsy).

That is, although early virological response was not enormously informative, "sustained virological response" (i.e. sustained low viral DNA levels over several years - even after a drug is stopped) did correlate well with reduced disease. Surprisingly, however, the initial studies suggest that reductions of 1000 fold in viral DNA levels (or greater) did not result in much better outcome than reductions of 100 fold. It appeared that reductions of 100 fold were the minimum needed (Mommeja-Marin et al, Hepatology 2003; 37:1309) for positive clinical outcomes.

Clearly, if the levels of viral DNA remain reduced after treatment is stopped, the likelihood of benefit (i.e. less liver disease) is the greatest.

Alternatives to liver biopsy for measuring a drug's benefit?
Serological (blood) assays are being studied that appear to offer alternatives to a liver biopsy and correlate well with biopsy information. It is important to note, however, that drugs with different mechanisms of action may require different surrogate markers.

Proteomics, a systematic examination of the compete protein profiles of the blood of HBV infected people, is being used and several promising, but as yet, unproved, protein markers have been discovered by HBF scientists and reported in scholarly journals. One of the most exciting results has been a "biomarker" that may help predict who is at greatest risk for liver cancer (in both HBV and HCV), which is under investigation by the National cancer Institute.

Other possible surrogate markers to consider for HBV are quantitative (amount of) and qualitative (type of) surface antigen (sAg) levels in the blood. These are easy things to measure and it certainly can be imagined that they would correlate with disease activity in the liver. Dr. DiBicesglie has already done work in this area and, again, the work was encouraging.
Finally, the type of viral DNA in the blood (not just amount) can probably be used as a surrogate marker. This includes detection of viral "cccDNA" (which is usually locked in the infected liver cell), viral mutants, and others.

Conclusions

The current consensus appears to be that for individual patients, clinicians still prefer to base a treatment decision on a liver biopsy. Nevertheless, there is a lot of hope and a clear momentum for the use of surrogate markers as a substitute for liver biopsy in the evaluation of a drug's efficacy (or effectiveness). It may now be possible to make compelling associations with clinical outcome for groups of patients based on a blood test.

Developing surrogate markers is critical in reducing the hassle and cost of getting a viral hepatitis drug approved by the U.S. Food and Drug Administration (FDA). Expediting the FDA drug approval process would be of enormous benefit to the entire hepatitis community.

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