

# BEST OF AASLD 2006

Highlights From the American Association for the Study of Liver Diseases 57th Annual Meeting and Postgraduate Course, October 27–31, 2006, Boston, Mass.

---

Reviewed by Nancy Reau, MD  
Assistant Professor of Medicine  
Section of Gastroenterology  
University of Chicago School of Medicine

## **Abstract 114** Sustained Biochemical and Virological Remission After Discontinuation of 4 to 5 Years of Adefovir Dipivoxil (ADV) Treatment in HBeAg-Negative Chronic Hepatitis B

Hadziyannis and associates sought to examine the durability of long-term treatment with adefovir (ADV) in patients with hepatitis Be antigen-negative (HBeAg-) chronic hepatitis B (CHB). Patients (n=33), who had been treated for 4 or 5 years with ADV and achieved persistent hepatitis B virus (HBV) DNA suppression and biochemical remission, underwent needle-core liver biopsy and then discontinued ADV therapy. All patients were followed-up monthly for the next 6 months, then every 3 months afterward. Serum samples at follow-up were tested via polymerase chain reaction to detect HBV DNA replication and evaluate for sustained viral response or relapse. Patients were followed for a median of 18 months. Three months after ADV discontinuation, 67% of patients had entered sustained remission lasting for a median of 17 additional months. HBV DNA levels became again detectable in all patients but at levels similar to the inactive hepatitis B surface antigen (HBsAg) carrier state (up to 50,000 copies/mL). Biochemical relapse without spontaneous remission has occurred in approximately one third of patients and was subsequently managed successfully with reintroduction of ADV therapy. The authors concluded that sustained virologic response (SVR) is achievable in HBeAg- CHB after discontinuation of 4 or 5 years of ADV therapy. In addition, after stopping ADV, approximately two thirds of these patients sustain, for a period of at least 15–20 months, normal alanine aminotransferase and low HBV DNA levels.

**NR** When evaluating a hepatitis B patient for treatment, one of the first distinctions pertains to HBeAg status. If a patient has Be antigen, seroconversion to HBe antibody is a measurable endpoint that may confer SVR and, thus, the possibility to discontinue therapy. In patients without Be antigen, there is no test to determine the durability of remission after therapy discontinuation. Even with adequate viral suppression reducing HBV DNA levels to a very low or negative number, previous studies have always shown that when therapy is stopped, viremia returns and enzymes elevate.

However, this may be a function of treatment duration as most of the published studies are pivotal trials, which are generally designed to compile information for a finite period of time. Most pivotal trials discontinue therapy after 12 months in patients with adequate treatment response. Response in HBeAg- patients is often considered enzyme normalization and viral suppression. In nearly all published trials, HBeAg- patients failed treatment discontinuation with resultant viral rebound and biochemical relapse. This is the very first study that has examined durability after 4 to 5 years of therapy in these patients and shown that a subset of them may achieve some degree of lasting response.

All of the patients in this trial became viremic again after discontinuation, but their final, stable viral levels were low, less than  $10^4$ . The REVEAL study demonstrated that increasing HBV DNA correlates with increasing hepatocellular cancer (HCC) risk, especially levels greater than  $10^4$ . After discontinuation of ADV, patients in the current study maintained levels much lower than their original baseline and lower than the perceived cancer risk threshold, which is encouraging. However, this population was unique. They had all been HBV DNA-negative for at least 4–5 years. They were not (and could not be) cirrhotic because discontinuation of therapy in a cirrhotic patient could result in disease flare and decompensation. Furthermore, there is no proof of long-term durability in these results. We cannot be sure that with time these patients will not develop disease progression. There is no long-term data regarding risk of HCC or any of the other long-term sequelae, though it certainly looks encouraging.

This abstract validates anecdotal reports of treatment discontinuation in optimal subsets of patients. However, this is not a practice that can be implemented without careful supervision. These patients must be continually monitored for viral and biochemical rebound with HBV DNA levels and transaminases, as well as screened for HCC. In addition, disease progression should be considered and may require repeat biopsy or noninvasive fibrosis markers for surveillance.

### **Abstract 782** Low Risk of HBV Recurrence Post-Liver Transplantation (OLT) in Patients Maintained on Nucleos(t)ide Analogue (NA) Therapy After Withdrawal of Hepatitis B Immune Globulin (HBIG)

Wong and colleagues examined the long-term risk of HBV recurrence in postorthotopic liver transplant (OLT) patients who had discontinued hepatitis B immune globulin (HBIG) therapy and were maintained on nucleos(t)ide analogs (NAs). They examined all patients at their transplant center who had received at least 7 intravenous doses of HBIG posttransplant with no HBV recurrence and had then withdrawn HBIG and been maintained on NA therapy. Of patients transplanted between January 1994 and December 2005, 21 met the inclusion criteria. In these patients, HBIG was discontinued at a median of 26.4 months post-OLT and median post-HBIG follow-up was 40.2 (4.5–51.1) months. During the HBIG therapy period, 15 patients received concomitant NA therapy with either lamivudine or ADV, whereas the other 6 were treated with HBIG monotherapy. All patients were negative for HBsAg and HBV DNA at the time of HBIG discontinuation. Of the patients studied, only 1 had HBV recurrence, after being lost to follow-up until Month 46 post-OLT, at which point he presented with fatigue and tested positive for HBsAg and HBV DNA. The authors concluded that HBIG discontinuation after 3 years post-OLT and maintenance on NA is associated with a very low risk of HBV recurrence in compliant patients.

**NR** This study addresses an important controversy because lifelong HBIG, although effective, is expensive and invasive, requiring intramuscular or intravenous administration once a month in the clinic. In addition, HBIG monotherapy is not completely effective, with a 30% HBV recurrence rate despite standard prophylaxis. Most HBIG failures relate to inadequate dosing; however, mutations may also emerge. Currently, HBIG is combined, posttransplant, with nucleos(t)ide and sometimes even combination therapy. The posttransplant treatment

regimen usually reflects the patient's pretransplant status. (Terrault et al. Management of the hepatitis B virus in the liver transplantation setting: A European and an American perspective. *Liver Transpl.* 2005;11:716-732). Typically if a patient's medication regimen was controlling the virus prior to transplant, it is continued after surgery. On the other hand, if the patient was significantly viremic prior to surgery, the risk of HBV recurrence is increased and the posttransplant regimen will reflect this. This is the patient who is most likely to receive combination therapy plus HBIG. The controversy arises when deciding the duration of therapy. The heightened concern for recurrent HBV commits the majority of patients to lifelong HBIG to prevent a small number of relapses.

Fulminant hepatic failure patients almost never experience recurrent hepatitis B after transplant. In these patients, there is most likely such an overwhelmingly strong immune response that not only does it kill the liver, it cures the virus or provides immune control over the virus. Patients with very low viral loads going into transplantation also have much lower risk of recurrence, whereas those with higher viral loads tend to have a much greater risk. It is unclear as to whether the Wong study stratified patients by pretransplant viral load, but it does demonstrate that discontinuing HBIG somewhere up to 3 years after initiation is safe in most patients transplanted with hepatitis B. Again, careful monitoring is vital.

This study is confirming a practice that is in wide use, though not universal. There are still centers that leave patients on HBIG for life. However, most centers maintain patients on oral nucleos(t)ides, and discontinue HBIG somewhere between 3 months and a year, depending on patient compliance and the risk of disease recurrence.

### **Abstract 588** Rapamycin Based Immunosuppression Leads to Prolonged Overall Survival After Liver Transplantation for Hepatocellular Carcinoma

Schumacher and associates developed a rapamycin-based immunosuppressive regimen for use in postliver transplant patients in the hopes of reducing the recurrence of HCC in these patients versus those treated posttransplant with calcineurin inhibitors. In this study, patients were included for analysis based on advanced (T3 or T4) pretransplant tumor stage and a minimum of 6 months continuous treatment with rapamycin. A total of 43 patients were followed, 22 receiving the rapamycin-based regimen and 21 the calcineurin regimen. Patients were retrospectively analyzed in pairs matched for tumor size, number of nod-

**Table 1.** Sustained Viral Response (SVR) With “High” Viral Load and “Low” Viral Load Using Different Cutoffs

	$\leq 400$ vs $>400 \times 10^3$ IU/mL		$\leq 600$ vs $>600 \times 10^3$ IU/mL		$\leq 800$ vs $>800 \times 10^3$ IU/mL	
n/N	90/129	189/439	112/177	167/391	156/206	156/362
SVR, %	70	43	63	43	60	43

ules, angioinvasion, and grading. Overall 5-year survival in the rapamycin-treated group was 85% versus 57% in the calcineurin inhibitor-treated group. Recurrence-free survival was 76% in the rapamycin-treated group versus 55% in the calcineurin group. The authors concluded that rapamycin appears to have a beneficial effect on long-term survival after liver transplant for HCC.

**NR** This is the first controlled trial that has demonstrated a benefit from rapamycin posttransplant. Rapamycin has been shown in the past to possess antiangiogenic properties and has decreased growth of HCC in cell cultures and animal tumor models. Subsequently, small case series suggested that rapamycin promoted tumor regression and decreased posttransplant HCC recurrence. However, until now there has not been, to my knowledge, a trial that compared a subset of transplant patients who received rapamycin versus a subset that did not and showed statistical benefit in the rapamycin group.

This is an important finding because we are beginning to push the envelope when it comes to transplantation for HCC. With effective antineoplastic agents like rapamycin, a larger subset of patients may be considered good organ recipients. (Kneteman NM et al. Sirolimus-based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma. *Liver Transpl.* 2004;10:1301-1311). The Milan criteria, which detail the number and size of lesions that are associated with acceptable patient outcomes, guide which patients can be listed and receive upgrade points to expedite transplantation. Currently, transplant candidates with HCC who fall outside of the Milan criteria-based United Network for Organ Sharing guidelines are not eligible for an optimal donor liver. They can consider being matched with a marginally compromised organ that reaches an acceptable level of viability; however, there are certainly ethical issues associated with this strategy. Several centers are investigating extended criteria. The resultant San Francisco criteria suggest that carefully picked patients outside of the Milan guidelines can be transplanted with equal outcomes. Rapamycin therapy may allow us to expand our patient pool further. However, the widened guidelines will not apply to all patients and donors. Recipients with metastatic

lesions or vascular invasion are unlikely to be considered for transplantation, regardless of cotherapy with an antineoplastic.

Despite the potential benefit, rapamycin is not free of side effects. Although it has less renal toxicity than traditional calcineurin inhibitors, it can still cause proteinuria and has been associated with mucositis, pulmonary problems, edema, and hepatic artery thrombosis. It actually has a black box label warning for use in liver transplantation and most centers will not use it in the first 3 months posttransplant due to concerns for wound healing and hepatic artery thrombosis, though they may consider adding it later.

#### **Abstract 209** Improving the Clinical Relevance of Pretreatment Viral Load as a Predictor of Sustained Virological Response (SVR) in Patients Infected with Hepatitis C Genotype 1 Treated With Peginterferon Alfa-2A (40KD) Plus Ribavirin

Zeuzem and coworkers conducted an analysis to evaluate the definitions of “high” and “low” viral load measures in genotype 1 chronic hepatitis C virus (HCV) patients that would be more meaningful in the current environment of pegylated interferon (PEG-IFN) plus ribavirin (RBV) combination therapy, especially with the recent conversion of viral load measurement from copies/mL to IU/mL. Treatment-naïve HCV genotype 1 patients (568) were retrospectively studied based on the results of 2 phase III trials of PEG-IFN $\alpha$ -2a (180  $\mu$ g/week) plus weight-based RBV (1,000–1,200 mg/day). The likelihood of achieving SVR was estimated as a function of baseline viral load strata and continuous variables (age, weight-based viral load, and pretreatment alanine aminotransferase quotient). Based on this model and receiver operating characteristic analyses, the baseline level that most effectively differentiated high and low probability of SVR was  $5.6 \log^{10}$  ( $\sim 400 \times 10^3$ ) IU/mL. Using this cutoff and characterization, 70% of baseline “low” viral load patients versus 43% of baseline “high” viral load patients achieved SVR (Table 1). The authors concluded that use of this cutoff point will allow treatment optimization in genotype 1 HCV patients.

**NR** One aspect of this study stems from the new mandate to standardize measurement and thus switch from viral copies per milliliter to international units per milliliter. Although polymerase chain reaction testing is a very sensitive test, it is not easily or reliably duplicated, particularly without a standard measure across labs. We will hopefully see a higher level of reproducibility with the standardization of international units.

The other important aspect of this study is the illustration of how “high” and “low” viral load definitions can affect expectations of treatment in hepatitis C and ultimately affect treatment course. At one time, we thought of HCV treatment as straightforward. Patients were stratified by genotype into 6- or 12-month treatment regimens.

Then, minor dosing modifications were made based on patient weight. Additional factors, including viral load, ethnic background, age, and presence or absence of cirrhosis, would affect the odds of achieving SVR but not necessarily the dose or duration of therapy.

Currently, there is so much validated information on the effect of these different factors that we are beginning to have the ability to individualize and optimize therapy. This revised division of “high” versus “low” viral load is the first in what will no doubt be a series of stratifications that may ultimately affect treatment dose and duration, attempts at retreatment, or even mode of treatment as new agents like protease and polymerase inhibitors become available.