

Approaches to Viral Hepatitis

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I am Paul Kwo from Indiana University. We are going to talk about viral hepatitis. I picked abstracts that reflect the current status of where we are for hepatitis C, abstracts that are going to most immediately impact your practice and then other ones that will help us treat our patients better with what I think are the currently available resources.

Abstract 222295: “Week 12 and beyond antiviral activity of higher doses of Albuferon combined with ribavirin in non-responders to prior interferon based therapy for chronic hepatitis C infection”

Albuferon™ is albumin fused to interferon alpha2b. The first novel aspect of this drug is that we can give this drug every two or four weeks which is nice. The side effect profile seems, based on preliminary data, to be amongst the most benign of the interferons. Subjects were randomized to three groups (900 mcg Q2W, 1200 mcg Q2W, or 1200 mcg Q4W) plus ribavirin 1000-1200 mg/d. After safety was demonstrated, two higher doses were enrolled (1500 and 1800 mcg Q2W). Sustained response rates at 48 weeks ranged from 20-25% for the lower doses. They show preliminary data for the higher doses going up to 1500 and 1800 mcg demonstrating that the viral loads went down even further. The 24-week response was predictive of the 48-week response. The important concept here is that there is going to be a limit to the efficacy of interferon, regardless of the type (fusion protein, pegylated, etc.). This fusion protein is a neat idea in that you manage to keep the serum interferon levels high. There do not appear to be dose accumulation issues with Albuferon™, so this might be a way to improve things in the future. We will have to see further data on SVR. The key aspects though, are dosing every two weeks, which is a very attractive way to administer interferon, and data suggest it is well tolerated, at least as good as the two pegylated interferons.

Abstract 220202: “Treatment of chronic hepatitis C in Thalassemic and Sickle Cell Disease. Patients with interferon Alfa2b (IFN) and ribavirin (RBV)”

Anemia is listed as a contraindication to ribavirin in hepatitis C. Ribavirin also causes hemolytic anemia. Therefore, patients with sickle cell and thalassemia have not been treated typically. This group treated 10 patients, five with sickle cell disease and five with thalassemia major (they get hepatitis C from repeated blood transfusion) with IFN monotherapy (N=2) or IFN plus ribavirin at decreased dose. They actually obtained very high sustained virologic response (60%) rates. Side effects were minimal and Hgb levels increased in the sickle cell patients. Now if you can get sustained response rates that are 60% for thalassemic patients, two with cirrhosis, and sickle cell patients, then we as clinicians should be able to offer treatment to this population of patients. Many sickle cell patients have hepatitis C and in fact, we have actually transplanted a couple of sickle cell patients with cirrhosis from hepatitis C. This is

encouraging for all of us to consider treating what we are going to call, the “special populations.” The potential toxicities of ribavirin have eliminated some of them from using this agent. Renal insufficiency patients are another group that we typically do not treat with ribavirin. Well, maybe we will be able to give small doses. It is here with adequate safety data, the small molecules such as protease and polymerase inhibitors may be better.

The question is when do we consider treating children for hepatitis C when they are on the list for transplant? In the United States, there are no guidelines for children so everyone must use their own judgment. Based on adult guidelines, in general, we like Child Pugh score no higher than B and MELD score no greater than 16. That is high to treat for hepatitis C. If they have poorly controlled ascites, I would not treat them. If they have severe neutropenia, I would not treat them. We try and get the ascites under control medically so there is none. We actually put the advanced cirrhotics who are awaiting transplant on spontaneous bacterial peritonitis (SBP) prophylaxis empirically. We get about a 20% sustained response rate in people awaiting transplant particularly if they have favorable genotype. We go out of our way to treat people with favorable genotypes prior to transplant simply because it is so much less of an issue post-transplant; it is much easier to treat. All you have to do though is get one bad infection in a cirrhotic patient on therapy to temper your enthusiasm. I am convinced that when you get neutropenic in the setting of decompensated cirrhosis, you are more prone to infections. We have had bad cellulitis; SBP, and fungemia as infections in patients on treatment, so you just have to be very, very cautious. Our cut-off is actually a MELD of about 16 for treatment.

Let me tell you how we have handled the hepatitis C transplant issue. Hepatitis C does recur almost universally. Ninety-nine percent of the time it reinfects the graft. Most of the time (90% of the time), the reinfection is actually just acute self-limited hepatitis of the new graft. About 10% of the time it becomes very ugly. You get cholestatic jaundice, and even progressive fibrosis. What we have evolved to is the following. We get liver biopsies at months 4 and 12 in all hepatitis C patients. In the journal *Hepatology* two months ago, there was a very nice article showing that just measuring the portosystemic gradient in post-transplant patients seemed to be just as accurate in predicting those who are going to get into trouble quickly. Again if you have fibrosis at month four, you need to start intervening then with interferon therapy. If you don't have fibrosis at month four, you could still choose to treat them but then you can sit tight. We biopsy everybody post-transplant with HCV infection at this time. We have also evolved to monotherapy as immunosuppression post transplant in HCV infection with just tacrolimus. We are steroid free. We don't use any corticosteroids other than intraoperative. I believe that the immunosuppression levels must be very steady the entire time. The Hepatitis C virus clearly does not like perturbations in immunosuppression and can become more active with significant changes in immunosuppression. You have heard much recently about how hepatitis C survival rates have dropped. There are probably two factors: one is that some of the donors are not as optimal as they used to be. You can solve this to some degree with short ischemia time. The other is that some of the newer anti-rejection medicines can cause problems. One of them is Mycophenolate or CellCept. It works fine in those with HCV infection if you don't change the dose. Hepatitis C is particularly sensitive to changes. Mycophenolate often gets added when you are not sure what is going on. Is it rejection? If we add it, usually it is that perturbation in my opinion that is the problem. We use Mycophenolate quite a bit in non-HCV infection and it is very useful when you want low doses of immunosuppression because of renal insufficiency and you want to add something. The trick is to keep it at a constant dose; do not keep varying it. When you taper immunosuppression you do it ever so gently. Also, if you think what you see is rejection on a liver biopsy, we never pulse with steroids anymore for hepatitis C. We joke in our biopsy conference meetings that corticosteroids are Purina hepatitis C chow. It loves the stuff and the viral levels go up by ten to one hundred fold as soon as you give a bolus of corticosteroids and then things get very difficult.

Abstract 225559: “Evaluation of a HCV patient support program’s impact on patient adherence”

Poor adherence to antiviral therapy is a common barrier to treatment success. Challenges associated with administration and tolerability make this issue especially true of pegylated interferons + ribavirin. The Be in Charge[®] program (BIC) is a comprehensive patient support program that encourages adherence by providing 24-hour inbound and proactive outbound on-call nursing support and mailings of HCV educational materials throughout therapy. The purpose was to determine the effect of BIC on patient adherence to peginterferon alfa-2b combination therapy (peg-2b). A retrospective cohort analysis comparing BIC enrollees to a matched control group was conducted. Filled prescription records were used to measure adherence based on the number of injections dispensed and proportion of patients who received an average of ≥ 1 injection per week during follow-up. The BIC program resulted in more prescription refills at 12, 24 and 48 weeks. More injections were refilled in the BIC group. The take home message here is that any support program is better. This one is particularly structured but I think there are many good ones out there. The more injections you take, the higher your chance of sustained virologic response. The important thing, when you sit down to treat a patient is that you have family members that get involved and you set realistic goals. The nurses are particularly good at identifying people who are going to help. I think that is an important aspect to helping people get through their therapy.

Question: Has anyone ever looked at outcomes in patients who are in a clinic that has dedicated resources and treats lots of patients, versus someone that is being cared for routinely in a center where they only treat a handful of patients, just to see what the difference is?

Answer: Yes, we separated out the hepatitis C centers of excellence who have been regularly participating in registration trials versus community doctors who have an interest in hepatitis C. We found that the sustained viral responses (SVRs) were higher in the people who are more experienced but only, interestingly, because of better compliance (less drop outs). Adverse events were the same, severe adverse events were the same, other treatment related side effects, and discontinuations were the same. Only patient non-compliance was different.

Abstract 220855: “Final analysis of virological outcomes and resistance during 5 Years of Adefovir Dipivoxil monotherapy in HBeAg-negative patients”

Adefovir is one of our choices for those with hepatitis B who require therapy. It does not seem to reduce the viral load as rapidly as lamivudine or entecavir, particularly entecavir. One of the advantages of adefovir is that it seems to have a much lower mutation rate. In this study they measured mutation rates, viral resistance, and those with elevated ALT followed for five years. At year two it was 3%, year three it was 11%, year five viral mutations were seen in 29%, 16% for mutations and virologic resistance and 11% for mutations, viral resistance, and elevated ALT. The treatment duration for E antigen negative HBV infected individuals at least with the nucleoside and nucleotide analogs is lifelong at this time. Many people say that hepatitis B oral therapies are very easy to start; they are very hard to stop. One of the things, I think, for which adefovir evolved was for the lamivudine resistant viruses. In hepatitis B you are going to find a couple of things with E antigen negative individuals. The first is that adefovir seems to be well tolerated up to five years and again this is important for hepatitis Be antigen negative, particularly with cirrhosis, cirrhosis may improve, particularly those with decompensated HBV and may even reverse in hepatitis B. This is well reported and with continued viral suppression you might be able to resolve ascites, and portal hypertension improves, that is all very important.

Abstract 221649: “Evolution of multi-drug resistant HBV: Implications on rescue therapy”

This is also very interesting. When you get a drug resistant mutation to hepatitis B, it is usually multiple. One set with lamivudine resistance, one with adefovir resistance, they are all on the same genome and that is a problem. We have a whole cohort of people who received lamivudine, and who developed YMDD motif resistant mutations. One thing we know is the faster you drive the virus down to zero the better off you are and that the less likely you are to develop resistance. A viral load of zero implies that there will be no mutation. One of the advantages of telbivudine is that it has very rapid inhibition of hepatitis B replication. The questions are if we decrease viral load quickly, will that translate into fewer mutations and will it also improve the antigen clearance rates? The jury is still out on that. It certainly is very potent. Entecavir is very potent in driving it down but does not perform nearly as well in the YMDD mutants. Other drugs you can use there include tenofovir, emtricitabine or Truvada and don't forget interferon where there are no resistance issues. There were two recent studies in *New England Journal of Medicine* showing that peg-interferon alpha2a did very well in both HBeAg positive and negative patients, as well as oral medicines without resistance issues.

Abstract 226569: “Can we predict advanced fibrosis in daily practice based on common blood tests”

This study compared liver biopsy to noninvasive tests to predict advanced fibrosis. There are several of them out there. There is Fibrospect, there is Fibroscore, and you now have the stiffness test. There is the APRI (AST platelet ratio index) which is the AST (aspartate aminotransferase) divided by platelet count and then there are a variety of other tests that are used to try and predict fibrosis. Liver biopsy isn't perfect. How many times have you had a biopsy come back on a patient you think is cirrhotic read as stage II or III scarring? You get a CT scan, see that the liver is nodular, but still your pathologist is insisting he/she does not see cirrhosis. These authors attempted to predict fibrosis using the APRI and what is called model III which looks like a complicated formula. Positive and negative predictive value were reasonable (0.70) for PRI >1.5. Eventually these are going to have greater clinical utility, but liver biopsy is not going away. Where are these non-invasive tests of best use in practice? I order them in people who are ambivalent about a biopsy. Though depending on your cutoff, they have high sensitivity and specificity, it is just a matter of whether or not you want to live with that degree of uncertainty. If we order one of these tests and you get a very high or low score, that is fairly reassuring because that is usually in the cutoff range where you can say, “It is very likely you don't have it or it is very likely you do have advanced fibrosis.” If you get an intermediate score, things get a lot more complicated and you can use that to help convince them to have a liver biopsy.

If you have a high APRI score, a low platelet count and an imaging study which shows splenomegaly, then you are fine. It is when you have a high APRI score, the CT scan is completely normal, platelet count is 200,000-300,000, the patient has palmar erythema, you are a little worried there is advanced fibrosis and they are ambivalent about therapy, it is there that I bring them back and say okay we really need to know. If you have no scarring and you don't want to be treated right now, if you have advanced scarring, we need to treat you now – that is how we try to use these non-invasive tests. I don't use this complicated model³ but it is interesting that people keep trying to search for a way to predict fibrosis using common blood tests. This formula is complicated and my prediction is unless there are resources such as Medmath or other PDA-type programs available, they will likely not be used.

Abstract 221577: “Impact of therapy of chronic hepatitis C (CHC) on quality of marital relationships”

This was something that I thought was interesting. The authors looked at divorce rates in this study and found that 13% of patients were separated or divorced during or shortly after therapy, with patients saying that part of this was related to hepatitis C. I don't think any of this is too surprising. When you start

treating people, in my opinion, you've got to know what the support system is to get the highest success. We actually insist that the significant other come in when we start treatment so that we know who is going to be helping them. It is interesting in the neuropsychiatric side effects, if you compare hepatitis B and hepatitis C there is much more depression in hepatitis C patients than in hepatitis B patients. If there is marital discord, I tell the patient to wait six months, get counseling and then come back.

Abstract 223760: “Employment status and work performance during therapy of chronic hepatitis C (CHC)”

This study confirms that CHC therapy (interferon or interferon plus ribavirin) results in discontinuation of employment and disability. To help, we actually send out a letter saying that the patient is going to initiate therapy and it may affect work performance. We ask employers to work with them as we try and help them get through this therapy. We fill out family medical leave act (FMLA) forms.

Some people will put off therapy for six to eight months because they have something major going on at work that they have to do. In an area of seasonal employment, people will want to get therapy after the summer starts. You see them in January or February they are not going to start therapy until September because psychologically they think they are not going to go to work. For people who have jobs requiring a high degree of concentration, there are a few antidepressants and other medicines that really help that. For instance, Wellbutrin anecdotally helps people who have to concentrate well during their jobs, such as accountants, lawyers, etc.

Abstract 214624: “Tenofovir (TNV) has a stronger antiviral effect than adefovir dipivoxil (ADV) against lamivudine (LAM) resistant hepatitis B virus (HBV)”

I predict that tenofovir will eventually replace adefovir as the therapy for hepatitis B. These were primarily Asians (N=109) resistant to lamivudine treated with TNV or ADV. There was no difference in E antigen loss, but viral reduction was far superior over a range of 13 to 17 months with TNV. No one has been able to show improvement in E antigen loss yet, which may be the key to effective therapy.

Abstract 213326: “Entecavir results in continued virologic and biochemical improvement and HBeAg seroconversion through 96 weeks of treatment in lamivudine-refractory, HBeAg(+) chronic hepatitis B patients (ETV-026)”

Entecavir is a very good drug. It gets the hepatitis B viral loads down well for naive, wild-type hepatitis B. It works wonderfully. Where its efficacy is a little bit less is in the lamivudine refractory patients. In this multicenter trial, patients refractory to lamivudine were randomized to entecavir versus continued lamivudine for 48 weeks. Those with SVR continued to 96 weeks. Entecavir is superior with regard to HBV DNA seroconversion. Thirty had undetectable HBV DNA out of 141 compared to 1/145 on lamivudine.

Question: Is there a population of hepatitis B that should say I really think you should go for interferon instead of oral medications?

Answer: The answer is yes. The population is hepatitis B, young, mildly elevated ALT level, not a lot of inflammatory activity and they are interested in being treated. Those are people you can certainly treat. For instance, all of you have seen the Asian data showing that a high hepatitis B viral load in Asians is associated with development of hepatocellular carcinoma. This was presented at DDW last year and they have also had several papers published on this. This is the Taiwanese cohort. We see a lot of Asians who are nervous about that. Their ALTs are relatively normal or barely elevated, biopsy showed minimal

inflammation and they say, “I want to get this virus down. I am worried that I am going to get liver cancer in two decades.” You tell them. “Treating you now, we may take a benign virus and create all kinds of drug resistant mutations that are going to make our ability to treat you later much worse.” I tell people, “If you want to try something, you could try interferon for a year.” The old interferon data showed that you used to have high ALT, low viral load with a 16-week course. With the pegylated interferon alpha2a and alpha2b you seem to be able to do just as well with nucleoside and nucleotide analogs and you don’t generate any drug resistant mutations. That is the advantage. If it doesn’t work you can say you tried and you are not stuck with potential of viral resistance later.

Abstract 225547: “Durability of HBeAg seroconversion following adefovir dipivoxil treatment for chronic hepatitis B (CHB)”

The question is for those of you who have treated hepatitis B and gotten a seroconversion, have any of you had someone relapse with reappearance of hepatitis B e antigen? It’s always frustrating when that happens. With Lamivudine, which is where most of the data comes from, you usually continue therapy for three to six months and stop after that. You usually have roughly an 85% chance of durable response when e antigen remains cleared. With adefovir they looked at the genotypes and found 91% durability after a follow-up of three years and almost all of the relapsers were HBV genotype C. So genotype C seems to have a higher relapse rate. What does this mean? It makes us wonder if genotype C might be one that requires longer duration of therapy once you seroconvert to try and help prevent relapse. This will have to be replicated with other studies. This was not compared to lamivudine, but it seems that just like lamivudine, the seroconversion is fairly durable. The other factor that is important in this study is that there did appear to be a shorter duration of HBV DNA undetectability. They received less adefovir, just 32 weeks, than those with durable seroconversion. Once you make them negative, you have to keep them negative for a period of time. It is similar to hepatitis C where you render them negative in the serum, there has to be a defined duration of therapy while it consolidates. For hepatitis B it is hard conceptually to understand what you are doing within the liver to prevent e antigen reappearance. It appears that 36 weeks or longer for adefovir therapy is required to reduce risk of relapse.

I think we will finish up there. Enjoy yourselves. Thank you.

Abstracts Discussed

222295: Week 12 and Beyond Antiviral Activity of Higher Doses of Albuferon Combined with Ribavirin in Non-Responders to Prior Interferon Based Therapy for Chronic Hepatitis C infection. *David Nelson, Vinod Rustgi, Vijay Balan, Mark Sulkowski, Louis Lambiase, Rolland Dickson, Russell Weisner, Gary Davis, Andy Muir, LuAnne Novello, Ren Yu, William Freimuth, Avidan Neumann, John McHutchison, Mani Subramanian*

Background and Aims: Albuferon (alb-IFN) is a novel recombinant protein consisting of IFN α genetically fused to human albumin. This ongoing Phase 2, dose-ranging study evaluates the safety and efficacy of alb-IFN in chronic HCV patients who were non-responders (failed to achieve EVR12 or clear HCV RNA on therapy) to previous IFN α based regimens. Methods: Subjects were randomized into 3 alb-IFN SC treatment cohorts (900 mcg Q2w, 1200 mcg Q2w or 1200 mcg Q4w) in combination with ribavirin (RBV) 1000-1200 mg/d. After evaluating safety data, 2 higher dose cohorts of alb-IFN 1500 mcg Q2w and 1800 mcg Q2w were enrolled. The treatment duration is 48w with 24w follow-up. The primary efficacy end-point is SVR. The initial 3 cohorts have completed 48w treatment and 12w data for the highest dose cohort is currently available. Results: Subject demographics and antiviral response for the 115 subjects enrolled are summarized in the table. At w12, the overall antiviral response in the 1800 mcg Q2w cohort was the highest despite having a greater proportion of prior PEG-IFN+RBV non-responders. The slope of HCV RNA decline at w4-12 was significantly more rapid (P<0.01) for the 1800 mcg cohort compared to the 900-1500 mcg cohorts in genotype 1, prior PEG-IFN+RBV non-responders. The w24 antiviral response was comparable across the 900-1500 mcg cohorts. Most patients who were RNA negative at w24 remained negative at w48. Antiviral response at w12 and w24 was predictive of w48 end-of-treatment response for the 900-1200 mcg cohorts. Overall, alb-IFN in combination with RBV was well tolerated and the safety profile in the 1500 mcg and 1800 mcg cohorts was comparable to the 900-1200 mcg cohorts in type, incidence and severity of AEs. Conclusions: Alb-IFN at doses up to 1800 mcg Q2w in combination with RBV is safe and demonstrates significant antiviral activity in prior IFN α non-responder patients. Further studies are warranted and are ongoing.

	900 μ g Q2w (n=23)	1200 μ g Q4w (n=24)	1200 μ g Q2w (n=24)	1500 μ g Q2w (n=22)	1800 μ g Q2w (n=22)
Demographics					
PEG-IFN+RBV NR	61%	63%	67%	68%	91%*
F3-F4 fibrosis (METAVIR)	30%	17%	29%	41%	32%
Median Baseline HCV RNA (log IU/ml)	7.1	6.2	6.6	7.0	7.6*
Antiviral response					
W12 Median HCV RNA reduction	2.1	1.5	1.7	1.8	3.7
EVR12 (≥ 2 log HCV RNA \downarrow)	12 (52%)	10 (42%)	10 (42%)	9 (41%)	13 (59%)
HCV RNA negative at w24	9 (39%)	6 (25%)	7 (29%)	7 (32%)	NA
End-of-treatment response at w48	8 (35%)	7 (29%)	6 (25%)	NA	NA

*P value <0.05 for comparison between 1800 μ g Q2 and other cohorts combined; NA = not available

220202: Treatment of Chronic Hepatitis C in Thalassaemic and Sickle Cell Disease Patients with Interferon Alfa2b (IFN) and Ribavirin(RBV) *David Bancel, Dominique Chaslin-Ferbus, xavier J Amiot, Isabelle Hagege, Jerome Schaeffer Plumet, Stanislas Pol, Robert Girot, jean-didier B grange*

Prognosis of patients with congenital haemolytic anaemia has greatly improved in recent years, particularly among those suffering from thalassaemic syndrome. In this population, hepatic complications due to post-transfusion viral hepatitis and iron overload become one of the main causes of death. The 1999 Consensus statement of the EASL listed anaemia as an absolute contra-indication to RBV in hepatitis C. Aim: to assess the efficacy and safety of IFN and RBV treatment among patients with congenital haemolytic anaemia **Methods:** Ten patients (mean age: 27.4 \pm 6.3 yr) were included: 5 sickle cell disease (4 treatment-naïve, 1 non responder) and 5 thalassaemic major patients (1 naïve, 4 non responders). Eight patients (5 sickle cell, 3 thalassaemic patients) were treated with PEGIFN and RBV. Two thalassaemic patients were treated with IFN monotherapy. PEGIFN was given at full dose. RBV was started with an undervalued dose (400mg/d), then progressively increased according to weight based recommended dose. Duration of treatment was 24 or 48 wk. **Results:** HCV genotypes were 1 and 4 in 8 cases. All sickle cell disease patients had a fibrosis METAVIR score ≤ 2 , whereas 4/5 thalassaemic patients were F4. A virological response at the end of treatment was achieved in 9/10 patients, and a sustained virological response (SVR) in 6/10 patients (3 thalassaemic patients including 2 with cirrhosis). Five of the six SVR were obtained with combination therapy. The 6 sustained responders did not present any hepatic complication during the follow-up. A non responding thalassaemic patient died of hepatocellular carcinoma recurrence after liver transplantation. The mean increase in transfusion requirements during treatment compared with the same period prior to treatment was 22% in thalassaemic patient group (growth factors were not administered). No sickle cell patient needed transfusion during or after treatment periods. Surprisingly, the haemoglobin level during and at the end of treatment was higher than the pretreatment value among 4/5 sickle cell patients (none of them being treated beforehand by hydroxyurea). **Conclusion :** In this pilot study, overall SVR was 60 %, despite the unfavourable genotypes of most patients. Combination therapy with IFN and RBV achieved a high SVR rate (62.5%, 5/8 patients). The increased transfusion requirements during treatment in thalassaemic patients are acceptable. Among sickle cell patients, no

previous case of excellent haematological tolerance under RBV and without hydroxyurea pre-treatment has been reported in literature: our data suggest the use of a full dose RBV and PEGINF from the start of treatment in these patients.

225559: Evaluation of a HCV Patient Support Program’s Impact on Patient Adherence. *Mohamed Hussein, Joshua S Benner, David Lee, Anne-Marie Sesti, David S Battleman*

Background: For patients with hepatitis C virus (HCV), poor adherence to antiviral therapy is a common barrier to treatment success. Challenges associated with administration and tolerability make this issue especially true of pegylated interferons + ribavirin. The Be In Charge® program (BIC) is a comprehensive patient support program for HCV patients; it encourages adherence by providing 24-hour inbound and proactive outbound on-call nursing support and mailings of HCV educational materials throughout therapy. **Objectives:** The purpose was to determine the effect of BIC on patient adherence to peginterferon alfa-2b combination therapy (peg-2b). **Methods:** A retrospective cohort analysis comparing BIC enrollees to a matched control group was conducted. Subjects were included if they were ≥18 years of age; started peg-2b on or after 1/1/2004; and could be followed for at least 12 weeks after treatment initiation. To reduce potential selection bias from self-enrollment in the program, BIC enrollees were propensity score-matched to peg-2b starters not enrolled in BIC (controls), based on clinical and demographic characteristics. Filled prescription records were used to measure adherence based on the number of injections dispensed and proportion of patients who received an average of ≥1 injection per week during follow-up. Adherence was compared using paired chi-square and t-test. **Results:** The BIC group consisted of 780 eligible subjects who were observable for ≥12 weeks, including 638 and 333 subjects observable for 24 and 48 weeks, respectively. Of control subjects, 8572, 7014, and 4071 subjects were observable for 12, 24, and 48 weeks, respectively. Compared to non-BIC subjects, BIC enrollees were more likely to be female (53% vs. 41%, P<0.0001) and to use injection delivery devices vs. vials (74.0% vs. 56.7%, P<0.0001). In the matched analysis, BIC subjects refilled 1.2 more injections (95% confidence interval [CI] 0.52, 1.83; P<0.0001) than the control cohort within 12 weeks, 2.7 more (95% CI 1.5, 3.8; P<0.0001) within 24 weeks, and 6.7 more (95% CI 4.3, 9.1; P<0.0001) within 48 weeks. Compared to matched controls, BIC enrollees were more likely to refill ≥12 injections within 12 weeks of initiation (72% vs. 64%, P=0.0005), ≥24 injections within 24 weeks (52% vs. 41%, P<0.0001), and ≥48 injections within 48 weeks (22% vs. 13%, P=0.0020). **Conclusion:** These findings suggest the BIC program significantly improves adherence to peg-2b. Additional research is needed to ascertain which aspects of the program are most effective and which patients are most likely to benefit from this intervention.

220855: Final Analysis of Virological Outcomes and Resistance During 5 Years of Adefovir Dipivoxil Monotherapy in HBeAg-Negative Patients. *Katyna Borroto-Esoda, Sarah Arterburn, Andrea Snow, Steven Chuck, Stefanos Hadziyannis, Stephen Locarnini, Fabien Zoulim, Jean-Michel Pawlotsky*

Background/Objectives: Treatment with adefovir dipivoxil (ADV) for up to 5 years provides clinical and histological improvement, but long-term therapy with HBV inhibitors can select for mutations in the HBV polymerase associated with resistance. Definitions of resistance have varied widely for different antivirals, making it difficult to compare incidence rates. **Methods:** We investigated the incidence and course of three categories of events in Study 438: 1) ADV-associated mutations regardless of HBV DNA level and ALT outcomes (“mutations”; M), 2) mutations with ≥1 log₁₀ copies/mL increase from nadir (confirmed or last measurement), or never suppressed to <4 log₁₀ copies/mL (“virologic resistance”; M+VR) or 3) mutations with virologic resistance and ALT elevations (ALT >1X ULN after normalizing ALT; M+VR+ALT). Patients were evaluated every 4 weeks (years 1+2) and every 3 months thereafter for HBV DNA (Roche PCR assays) and ALT. Sequencing was performed yearly on all samples with detectable HBV DNA. **Results:** Over five years, 29 patients developed mutations (M) in HBV polymerase associated with ADV resistance (rtN236T and/or rtA181V). Eighteen patients with mutations experienced virologic resistance (M+VR). The median time of follow-up on ADV monotherapy was 36 weeks in these patients compared to 12 weeks in those who had mutations without virologic resistance. Thirteen patients had virologic resistance and ALT elevations (M+VR+ALT). The median time of follow-up on ADV monotherapy was 36 weeks in these patients compared to 18 weeks in the patients without ALT elevations. Eleven patients received lamivudine therapy (monotherapy or in addition to ongoing ADV) subsequent to development of ADV mutations which resulted in a 2-6 log₁₀ drop in HBV DNA. **Conclusions:** At five years, monotherapy with ADV in HBeAg-negative patients results in cumulative rates of 29% for mutations, 16% for mutations and virologic resistance, and 11% for mutations, virologic resistance, and ALT elevations.

Cumulative Probabilities of Virological Outcomes Calculated by Life-Table Analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
M	0%	3%	11%	18%	29%
M+VR	0%	3%	8%	13%	16%
M+VR+ALT	0%	2%	6%	10%	11%

221649: Evolution of Multi-Drug Resistant HBV: Implications on Rescue Therapy. *Hyung Joon Yim, Munira Hussain, Stephen Wong, Ying Liu, Scott K Fung, Anna S Lok*

Background: Multi-drug resistant HBV have been reported in patients who received sequential treatment with nucleoside monotherapy. In vitro studies showed that HBV constructs with mutations resistant to lamivudine (LAM) and adefovir (ADV) have marked reduction in sensitivity to combination of LAM+ADV, while constructs with mutations resistant to either drug remain sensitive to the other drug. Aims: To determine if mutations conferring resistance to multiple antiviral agents are present on the same HBV genome in vivo and to describe the evolution of these mutations. Methods: Sera from 6 patients found to have dual-resistant HBV mutations on direct sequencing were cloned after nested PCR, 18-20 clones from each sample were sequenced. Results: Mutations to both therapies were present on the same genome in 163/195 (84%) clones from 10 samples with dual-resistant mutations to LAM+ADV, LAM+HBIG, or LAM+entecavir (ETV) on direct sequencing, 32 (16%) clones had mutations to one drug. Evolution of mutations was examined in 3 patients. Patient 1 received LAM+ETV after LAM breakthrough, all 18 clones had L180M and M204V/I at month 0 (start of ETV), clonal analysis first detected ETV-resistant mutation (T184L) at month 20, 6 months earlier than direct sequencing. Both treatments were stopped at month 34 (T184L: 20/20 clones); 6 months later, T184L was detected in 12/20 clones while L180M and M204V/I remained detectable in 19/20 clones. Patient 2 was switched to ETV monotherapy after LAM breakthrough, all 20 clones had L180M+M204V at month 0. At month 36, ETV-resistant mutation I169T was detected in 15 and S202G in 4 clones. At month 41, S202G was present in 17 clones and I169T in 4 clones, LAM-resistant mutations remained detectable in all 20 clones. Patient 3 developed HBV recurrence after transplant despite receiving LAM+HBIG. All 18 clones had M204I and sG145R when HBV recurrence was diagnosed. ADV was added and LAM stopped 7 months later. ADV breakthrough occurred after 41 months of ADV when all 18 clones had ADV-resistant N236T. Four months after reintroduction of LAM, all 20 clones had L180M+M204V, 12 clones had additional V173L change. However, N236T was replaced by a different ADV-resistant mutation P237H. Conclusions: Our study showed that mutations conferring resistance to multiple antiviral agents are present on the same viral genome, suggesting that combination therapy directed against mutants resistant to each treatment may not be adequate in suppressing dual-resistant HBV. Sequential antiviral therapy leads to selection of multi-resistant HBV; mutations evolve during continued treatment resulting in mutants with increased replication fitness.

226569: Can We Predict Advanced Fibrosis in Daily Practice Based on Common Blood Tests? *Ramsey Cheung, Sue Currie, Hui Shen, Timothy Morgan, Ke-Qin Hu, Samuel Ho, Norbert Brau, Edmund Bini, Teresa Wright*

Background: Several indexes based on simple lab tests correlated with liver biopsies read by expert pathologists in highly selected settings; applicability to less stringent, community-based practice is unclear. Aim: To compare the specificity, sensitivity and ROC of these indexes with liver biopsies in a cohort of 548 veterans with chronic hepatitis C from 24 centers nationwide enrolled in a previous study. Method: All lab tests including interpretation of the liver biopsy were done locally. The following indexes were calculated and correlated with a 5-point fibrosis stage (F0-F4): platelet <100 x10⁹/L, AAR (AST/ALT), Pohl score (positive if AAR>1 and platelet <150x10⁹/L), APRI ([AST/ULN]/platelet [x10⁹/L]x100, and “Model 3” (log odds [predicting cirrhosis]= -5.56-0.0089 x platelet (x10³/mm³)+1.26xAAR+5.27xINR) (Lok et al, 2005). Results: This cohort was predominately male with 24% blacks, and distribution fibrosis stage of 0,1,2,3,4 were 11%,24%,28%,24%,13%, respectively. When patients with mild fibrosis (F0-2) were compared to those with advanced fibrosis (F3-4), the area under the ROC were 0.531 for platelet count alone, 0.527 for AAR, 0.537 for Pohl score, 0.746 for APRI and 0.754 for model 3. Recent alcohol use within 12 months did not affect the performance of these models. Conclusions: AAR, Pohl and platelet counts have limited ability to predict advanced fibrosis when compared to liver biopsy. However, APRI > 1.5 has a high negative predictive and positive predictive value (0.71 and 0.70). In addition, the newly described model 3 with cutoff value of <0.2 has a high sensitivity for excluding and >0.5 has high specificity for predicting advanced fibrosis. These scoring systems may be useful in daily clinical practice and deserve further prospective validation studies.

Predicting advanced fibrosis (F3-4)

Variable Name	Sensitivity	95% CI of Sensitivity	Specificity	95% CI of specificity	Positive predictive value	95% CI of PPV	Negative predictive value	95% CI of NPPV
AAR>=1.0	0.217	0.163-0.282	0.798	0.749-0.839	0.391	0.301-0.489	0.630	0.582-0.676
Pohl score	0.096	0.060-0.148	0.979	0.955-0.991	0.731	0.520-0.877	0.644	0.600-0.686
APRI<0.5	0.123	0.082-0.177	0.631	0.577-0.682	0.165	0.111-0.235	0.548	0.498-0.598
APRI>=1.5	0.376	0.307-0.443	0.904	0.867-0.932	0.697	0.601-0.780	0.708	0.663-0.750

APRI<1.0	0.397	0.330-0.468	0.204	0.163-0.251	0.228	0.186-0.276	0.363	0.296-0.435
APRI>=2.0	0.235	0.180-0.300	0.939	0.907-0.961	0.696	0.572-0.798	0.674	0.630-0.716
Model 3 <0.2*	0.931	0.884-0.962	0.321	0.270-0.376	0.454	0.404-0.505	0.886	0.810-0.936
Model 3 >0.5	0.508	0.435-0.581	0.848	0.802-0.885	0.669	0.585-0.744	0.740	0.691-0.784

* exclude advanced fibrosis

221577: Impact of Therapy of Chronic Hepatitis C (CHC) on Quality of Marital Relationships. *Miechelle O'Brien, Lawrence S Rosenthal, Edward Lebovics*

BACKGROUND: Impairment of quality of life by therapy of CHC has been documented in studies utilizing validated social science questionnaires. Specific impact on close valued relationships such as marital or significant others has not been examined. **METHODS:** Questionnaires were sent to 445 consecutive patients treated with either interferon-alpha 2b or pegylated interferon plus ribavirin. Questions addressed communication within the relationship, sexual intimacy, ability to share household responsibilities, quality of shared leisure time, arguing, and overall quality of the marriage prior to treatment initiation, during treatment, and after treatment completion. Responses were scored on a scale of 1 to 5, with 5 being the highest functioning. Also, patients were asked whether they separated or divorced during or shortly after their treatment and if this was attributable to therapy. **RESULTS:** Of 114 respondents, 15 patients (13.1%) were either separated (n=10; 8.8%), or divorced (n=5; 4.4%) during or shortly after treatment. Six of the 10 who separated and 2 of the 5 who divorced stated this was in part secondary to CHC therapy. Mean scores for all parameters assessing aspects of the marital relationship significantly decreased from baseline to during therapy (p<0.001 for each) and returned to baseline after therapy. 35% of patients had no impairment in communication, 49% had a drop of 1-2 points, and 12% a drop of 3-4 points. 30% reported no change in sexual intimacy, 50% had a drop of 1-2 points, and 19% a drop of 3-4 points. 27% reported no change in sharing household responsibilities, 48% had a drop of 1-2 points, and 23% a drop of 3-4 points. 29% reported no change in quality leisure time spent with spouse, 32% had a drop of 1-2 points, and 16% a drop of 3-4 points. 49% reported no change in frequency of tense arguments with significant other, 37% had a drop of 1-2 points, and 7% a drop of 3-4 points. 53% reported no impairment in overall quality of marriage, 37% had a drop of 1-2 points, and 7% a drop of 3-4 points. **CONCLUSIONS:** CHC therapy impairs marital relations and may contribute to separation and divorce. Patients should be counseled prior to initiation of therapy of these potentially life altering effects, and appropriate care taken to prevent such outcomes.

223760: Employment Status and Work Performance during Therapy of Chronic Hepatitis C (CHC). *Miechelle L O'Brien, Lawrence S Rosenthal, Edward Lebovics*

BACKGROUND Impairment of quality of life by therapy of CHC has been documented in studies utilizing validated social science questionnaires. Impact on work performance is ill-defined. **METHODS** Questionnaires were sent to 445 consecutive patients who underwent treatment with either interferon alpha 2b or pegylated interferon plus ribavirin. Six questions addressed ability to concentrate at work and cope with job stress, work stamina, perception of evaluation by superiors, absenteeism, and overall quality of work performed. Responses were scored 1 to 5 (very poor/poor/fair/good/excellent) for before, during, and after treatment. Also, patients were asked whether they discontinued work (fired/quit/disability leave) and whether CHC therapy contributed to any change in employment status. **RESULTS** 116 patients responded. Among this group, 30 (26%) were either fired (n=6, 5%), quit (n=2, 2%) or took disability leave (n=22, 19%) from their jobs during CHC treatment. All patients who were fired or quit and 86% of those who took leave attributed their change in employment status to adverse effects of CHC therapy. Mean baseline scores (prior to CHC therapy) for each of the 6 work performance questions was between 4 and 5. During therapy, mean scores for each question dropped to between 2 and 3 (p<.001). Scores returned to baseline levels after therapy. Of note, 59% of patients reported that CHC therapy caused a decline in their overall work performance. **CONCLUSIONS** In this series CHC therapy was associated with a 26% rate of discontinuation of employment due to either termination or temporary disability leave. 59% of patients reported a significant impairment of overall work performance. On the whole, there was no perception of work performance impairment at baseline and after therapy was completed. Patients should be counseled accordingly prior to initiation of therapy.

214624: Tenofovir(TNV) has a stronger antiviral effect than adefovir dipivoxil(ADV) against lamivudine(LAM) resistant hepatitis B virus(HBV). *Hie-Won L Hann, hee Bok Chae, Stephen R Dunn*

Patients with chronic hepatitis B (CHB) who developed LAM resistance were treated with TNV or ADV. In some, LAM was continued or added later. In this retrospective study we compared the suppressive activities of TNV and ADV against LAM resistant HBV. **Materials and Methods:** 109 patients (86 M, 23 F), all Asian Americans except 1 Caucasian male, were included

in the study. All had viral breakthrough during LAM therapy and received TNV or ADV for ≥ 6 months (mos). Reduction of HBV DNA and ALT normalization were assessed at 6 and 12 mos. HBeAg loss was examined within 24 mos. Results: 44 patients (37M, 7F) received TNV (12 with LAM) and 65 (49M, 16F) received ADV (18 with LAM). Median ages for TNV and ADV groups (grps) were 49 years (32-68) and 45 years (22-68) respectively. Median duration of therapy was 13 mos (ranges 6-38) for TNV grp and 17 mos (ranges 6-34) for ADV grp. Baseline ALT levels (IU/L) were 77.0 ± 86.2 and 100.4 ± 195.0 for TNV and ADV ($P=0.46$). As shown in the table, baseline HBV DNA levels were similar for both grps. Mean HBV DNA reduction (Log₁₀ copies/ml) at 6 and 12 mos was stronger for TNV than ADV. Viral reduction >3 log (at 12 mos) was greater for TNV than ADV. HBeAg loss in 24 mos showed no difference. ALT normalization (6 mos) was 55% and 66% for TNV and ADV respectively. Using single factor, two-tailed ANOVA, 4 grps, TNV (n=32), TNV+LAM (n=12), ADV (n=47) and ADV+LAM (n=18), were compared. There was no difference in 4 grps with respect to the baseline DNA or baseline ALT. However, HBV DNA reduction at 6 mos was greater for TNV+LAM grp than either ADV grps. Furthermore, no patient developed viral breakthrough during the 6- 38 mos observation period. Conclusion: Our results suggest that for LAM resistant HBV, TNV, alone or combined with LAM exerts a greater viral reduction than ADV. However, there is no difference in HBeAg loss or ALT normalization. It appears that stronger HBV DNA reduction may not necessarily speed up the HBeAg loss. Viral breakthrough appears low with TNV with or without LAM.

	TNV	ADV	p value
No. Pts	44 (12 with LAM)	65 (18 with LAM)	
Duration of Treatment	13 mos (6-38)	17 mos (6-34)	
Baseline HBV DNA (log ₁₀ copies/ml)	6.23+/-1.66	6.49+/-1.56	0.404
Mean HBV DNA log reduction (6 mos)	3.65+/-1.75 (n=30)	1.94+/-1.98 (n=45)	0.00
Mean HBV DNA log reduction(12 mos)	5.03+/-1.64 (n=15)	2.36+/-2.37 (n=42)	0.00
DNA reduction >3 log	63%	28%	0.013
HBeAg loss (in 24 mos)	4.5% (2/44)	7.7% (5/65)	0.699

225547: Durability of HBeAg Seroconversion Following Adefovir Dipivoxil Treatment for Chronic Hepatitis B (CHB).
Ting-Tsung Chang, Mitchell L Shiffman, Myron Tong, Yun Fan Liaw, Piyawat Komolmit, Jeff Sorbel, Sarah Arterburn, Elsa Mondou, Steven Chuck, Patrick Marcellin

Background and aims: HBeAg seroconversion (HBeAg loss with development of anti-HBe) has been considered an important therapeutic marker in the treatment of CHB in HBeAg+ patients. Study 481 evaluated the durability of seroconversion following adefovir dipivoxil (ADV) treatment. Methods: Study 481 enrolled CHB patients with compensated liver function who had confirmed seroconversion to anti-HBe and HBV DNA $< 100,000$ copies/mL by Roche Amplicor PCR assay during treatment with adefovir dipivoxil 10 mg once daily. Patients were followed off treatment with serologic assessments at least every 24 weeks. Results: At entry (n=45) median age was 34 years, 64% male, 73% Asian, 27% Caucasian, median serum HBV DNA 3.00 log copies/mL (min-max, 2.6, 3.2), and median ALT 25 IU/L (min-max, 9,110). Median duration of ADV treatment before seroconversion was 54.4 weeks (Q1, Q3; 24.1, 75.4) and after seroconversion was 37 weeks (Q1, Q3; 27.0, 72.1). Median follow-up off drug was 143 weeks (Q1, Q3, 110, 193; range 13-245). Four patients (9%) did not maintain seroconversion at follow-up weeks 12 (n=3) and 16 (n=1) (at the time of seroreversion all had HBV DNA $>100,000$ copies/mL; ALT 84-222 IU/L). Forty-one patients (91%) maintained durable seroconversion at the last 2 assessments and most were followed for several years: 15 (37%) for 2-3 years and 19 (46%) for over 3 years. There was no difference in entry characteristics (serum HBV DNA, ALT, age, gender) for patients with and without durable seroconversion. Median duration of ADV treatment before seroconversion was longer (108 versus 48 weeks) for patients who seroreverted. Seroreverters received less ADV after seroconversion than those with durable seroconversion (median 22 versus 41 weeks). All 4 seroreverters were Asian and all had HBV genotype C. The distribution of genotype among durable seroconverters was 10 A; 9 B; 17 C; 4 D; 1 G. For all patients, the median HBV DNA at the last timepoint off drug was 3.04 log copies/mL (Q1, Q3; 3.00, 4.15; 44% < 1000 copies/mL), and median absolute ALT was 28 IU/mL (Q1, Q3; 21, 41). Conclusions: Seroconversion to anti-HBe was durable off ADV treatment in 91% of patients over a median follow-up of 3 years. Four patients (9%) lost seroconversion and reverted to HBeAg+ within 16 weeks of the end of treatment; these 4 patients were genotype C and received less ADV after seroconversion (maximum 32 weeks) than patients with durable seroconversion

Additional Reading: Approaches to Viral Hepatitis

216074: Delaying Gastric Emptying and Enhancing Cholecystokinin Release and Satiety by Using Acid Stable Fat Emulsions. Luca Marciari, Martin Wickham, Gulzar Singh, Debbie Bush, Barbara Pick, Eleanor Cox, Annette Fillery-Travis, Richard Faulks, Charles Marsden, Penny A Gowland, Robin C Spiller

Background: Consumer preferences are leading to a steady increase in consumption of convenience foods which often contain highly palatable fat as an emulsion. We have previously shown that oil/water emulsions can rapidly separate in the acid gastric environment leading to layering of fat. This caused rapid emptying of the resulting low fat aqueous phase with rapid reduction of gastric distension and satiation. We hypothesised that stabilising an emulsion would prevent intragastric fat layering and, by ensuring prolonged exposure of duodenal receptors to fat emulsion, maximise cholecystokinin (CCK) release, delay gastric emptying and prolong satiety. **Aims:** To investigate in healthy volunteers the effect of modifying the intragastric acid stability of equicaloric fat emulsions on gastric emptying, CCK levels and satiety. **Methods:** 9 healthy male volunteers attended on 2 separate days, having fasted overnight. They were fed 500 mL of one of two olive oil-in-water emulsion test meals with equal fat content (675kcal) and equal droplet size distributions, but opposite acid stability. One remained intact when exposed to the stomach acidic conditions (“acid-stable”) and the other (“acid-unstable”) broke rapidly on being acidified yielding a layer of oil floating above an aqueous phase. Serial measurements of gastric volumes (using magnetic resonance imaging, MRI), plasma CCK (using radioimmunoassays) and satiety feelings (using self-assessment questionnaires) were made for 10 hours. **Results:** (mean±SEM) MRI images showed a layering of oil which became apparent soon after ingestion of the unstable emulsion but was not seen with the acid stable emulsion. This was associated with a faster gastric half-emptying time for the acid-unstable (72±13 min) compared with the acid-stable emulsion meal (171±35 min), Wilcoxon’s $p < 0.008$. The acid-unstable emulsion released less CCK than the acid-stable one (AUC 531±111 versus 1095±244 pmolmin/L), $p < 0.001$. An overall exponential correlation between decreasing hunger with increasing CCK plasma level was found ($r=0.91$), with the acid-stable emulsion being associated with greater satiety and higher CCK levels. **Conclusion:** Rendering fat emulsions stable to gastric acid is a simple way of enhancing satiety by a combination of delaying gastric emptying and enhancing blood levels of CCK. Modifying food production methods to manipulate the post-prandial delivery of fats to the intestine, the gut peptides response and hence satiety, could aid in the prevention as well as treatment of obesity. Funded by BBSRC.

220490: Predicting Liver Disease Complications (HCC And Cirrhosis) In Patients With Chronic Hepatitis B Infection Using A Risk Function Model: The R.E.V.E.A.L.- HBV Study. Chien-Jen Chen, Hwai-I Yang, Uche H Iloeje, Chin-Lan Jen, San-Lin You, Yun-Fan Liaw

Background & Aims: Predicting CHB patients at risk of progressing to liver complications is a clinical challenge. Our objective was to develop a prediction model using readily available non-invasive clinical information in CHB infected subjects. **Methods:** Information from HBsAg-positive (anti-HCV-negative) subjects recruited from 7 townships in Taiwan between 1991 and 1992 was used for these analyses. Subjects were randomized into two groups (training and validation) on a 1:1 basis. HCC and cirrhosis cases were ascertained via computerized linkage to the Taiwanese National Cancer Registry and Death Certificates Profiles or by ultrasound examination. Additionally, medical charts were reviewed using a structured abstraction form to confirm the diagnoses. HCC was confirmed by one of the following: cyto-histopathology; focal liver lesions by two coincident imaging studies (ultrasonography, CT Scan, MRI and/or angiography); focal liver lesion on one imaging study and an alpha fetoprotein (AFP) level >400 ng/mL. Multivariate logistic regression models were used to identify the predictive variables, and the model accuracy determined by the Area Under the Receiver Operator Characteristic curves (AUROC). **Results:** N=3582/3653 without baseline cirrhosis were included. The mean follow-up time was 11 years. The training set 1791/3582 (50%), was comparable to the validation set for all variables and outcome events ($p > 0.05$). The best fitting models had Age and HBV DNA as the strongest predictors of future liver complications. For HCC only model AUROC=0.8450; concordant percent 96.4%; discordant percent 3.6%; model goodness of fit $p=0.49$. The risk (OR [95% CI]) associated with age 60-65 was 17.5 [6.4-47.5] [reference group 30-39]; and HBV DNA ≥ 105 copies/mL was 8.9[4-19.9] [reference <300 copies/mL]. For HCC/cirrhosis model AUROC=0.7713; concordant percent 88.5%; discordant percent 11.5%; model goodness of fit $p=0.71$. The risk (OR [95% CI]) associated with age 60-65 was 4.3 [2.5-7.5] [reference group 30-39]; and HBV DNA ≥ 105 copies/mL was 4.9 [3.3-7.5] [reference <300 copies/mL]. AUROC in the validation group was 0.86 (HCC model); 0.79 (HCC/cirrhosis model). **Conclusion:** Risk stratification for liver disease complications in CHB-infected persons is possible using a model comprised of readily available non-invasive clinical information. This model may be useful in making management decisions.

221267: FMRI Correlates of Pathologically Changed Alpha Rhythm in Patients with Hepatic Encephalopathy. Petra Ritter, Matthias Moosmann, Esmatollah Kasim, Elke-Tatjana Schuetz, Herbert Lochs, Arno Villinger, Johann Ockenga

Objective: The simultaneous combination of EEG and fMRI has recently been shown to be capable of providing maps which are functionally related to the classical posterior alpha rhythm in healthy subjects. It has been reported that patients with hepatic

encephalopathy have altered topography of EEG background rhythms. The aim of this study was to investigate fMRI correlates of pathologically changed alpha activity in patients with hepatic encephalopathy. Methods: Ten patients with liver cirrhosis (8 alcoholic; 1 PBC; 1 HCV; 5 Child A; 3 Child B; 2 Child C; age: 47.2±4.3 years) were included. Patients were lying in the dark bore of a 1.5 T MR tomograph. EEG was recorded from 29 scalp positions using an MR-compatible EEG amplifier and 32 channel EEG cap including one EOG and two ECG electrodes. Patients were asked to stay awake and to be relaxed with eyes closed during the whole experiment. No other task was provided. Functional MRI (BOLD sensitive gradient echo planar imaging sequence, TR=2 s, TA=1650 ms, 16 slices) and EEG (sampling frequency 5000 Hz) were acquired simultaneously. To obtain continuous EEG signal, artifacts related to MR-acquisition were corrected using an algorithm proposed by Allen. Additionally, the severity of hepatic encephalopathy was analyzed by 5 usually applied psychometric paper-pencil tests. Results & Discussion: Psychometric test results ranged from 1 to -13 (mean±SD: 5±3.3) detecting subclinical hepatic encephalopathy in 5 patients. SPM group analysis (random effects N=10) yielded significant (p<0.01, uncorrected) alpha rhythm associated negative BOLD signal in the occipital cortex which is in concordance with former results by our and other groups. However, alpha activity associated negative BOLD signal in the patients group was maximal in the frontal cortex bilaterally, where no significant signal was found for healthy subjects. These results agree with electrophysiological findings of a anteriorized alpha rhythm in patients with hepatic encephalopathy. Conclusions: Simultaneous EEG-fMRI provides maps of areas which are involved in alpha rhythm generation. An occipital-to-frontal shift of alpha activity in patients with hepatic encephalopathy is associated with an occipital-to-frontal shift of maximal negative BOLD signal in fMRI.

221475: Diagnostic Liver Biopsy in Patients with Advanced Fibrosis and Cirrhosis. *Kenneth E Sherman, Zachary D Goodman, Sara T Sullivan, Sima Faris-Young*

Liver biopsy is a key modality in the diagnosis and staging of liver disease. However, optimal biopsy technique in cirrhotic subjects whose samples are prone to fragmentation and suboptimal interpretation has not been established. We evaluated the effect of biopsy technique on specimen size, quality and other features in 923 biopsies in patients with advanced fibrosis/cirrhosis due to HCV infection. METHODS: Liver biopsy specimens were obtained during the course of a phase II, double-blind randomized placebo controlled multicenter trial designed to determine the safety and efficacy of interferon-gamma 1b in patients with hepatitis C (HCV) associated severe liver fibrosis or cirrhosis (Ishak stages 4-6). The investigators at individual sites were permitted to choose the approach and type of liver biopsy performed, but the protocol specified that specimens should be at least 20 mm in length, to ensure adequate sampling for evaluation of fibrosis. Biopsies were centrally reviewed. The following definitions were utilized: Adequate ≥ 6 portal tracts, Marginal 3-5 portal tracts, Inadequate ≤ 3 portal tracts. RESULTS: Needle type was reported in 826 cases. Cutting needles were used for 595 of the biopsies (69.7%), aspiration needles for 250 (30%), while the remainder was unknown or another method. Fragmentation was observed in 39.2% of liver biopsies obtained using an aspiration technique, but in only 4.7% of samples collected using an automated cutting needle (p<0.001). Biopsies performed with automated cutting needles were judged to be adequate in 553 (93%), marginally adequate in 36 (6%) and inadequate in 6 (1%). Aspiration biopsies were adequate in 207 (83%), marginal in 37 (15%) and inadequate in 6 (2%). Statistically, aspiration methods were much more likely to be judged inadequate than automated cutting needle techniques (p=0.005). Mean biopsy length was 19.17 mm (SEM ± 0.31) across 886 biopsies evaluated. Mean length was 17.47 mm (S.E.M. ± 0.52) for aspiration biopsies, 20.26 mm (S.E.M. ± 0.37) for automated cutting needle biopsies, and 16.75 mm for other biopsy types. Analysis of variance indicates that automated cutting needles produced significant longer biopsies than other types (p<0.05). There were no serious adverse events associated with liver biopsy in any subject and no procedure related mortality. CONCLUSION: Biopsy in advanced liver disease more often yields larger, unfragmented samples amenable to pathologic interpretation when performed with an automated cutting needle compared to aspiration (suction) biopsy. Adoption of this technique would facilitate accurate biopsy evaluation in patients with advanced fibrosis/cirrhosis.

225822: Valopicitabine (NM283), Alone or with Peg-Interferon, Compared to Peg Interferon/Ribavirin (pegIFN/RBV) Retreatment in Hepatitis C Patients with Prior Non-Response to PegIFN/RBV: Week 24 Results. *Paul Pockros, Christopher O'Brien, Eliot Godofsky, Maribel Rodriguez-Torres, Nezam Afdhal, S Chris Pappas, Eric Lawitz, Natalie Bzowej, Vinod Rustgi, Mark Sulkowski, Kenneth Sherman, Ira Jacobson, George Chao, Steven Knox, Keith Pietropaolo, Nathaniel Brown*

Background: HCV genotype 1 non-responders (NR) to pegIFN/RBV comprise over 50% of currently treated patients and have no proven treatment options. NM283 has shown anti-HCV activity alone and in combination with pegIFN in Phase I-IIa trials, without viral breakthrough for study periods up to 6 months. Methods: This ongoing Phase IIb trial is comparing 5 treatments in NR patients with HCV-genotype 1, whose HCV RNA never became PCR-negative with ≥ 12 weeks of pegIFN/RBV. All patients had HCV RNA ≥ 5 log₁₀ IU/mL by TaqMan PCR, ALT<5xULN, and compensated disease. Patients were randomized 1:2:2:2:2 among 5 treatments: NM283 monotherapy (800 mg/d), 3 combination (comboRx) arms with different NM283 dosing (400 mg/d; 800 mg/d; or dose-ramping 400 to 800 mg/d) +pegIFN, or pegIFN/RBV retreatment as control. PegIFN-2a is dosed at 180 µg SQ/week with weight-based RBV (1000-1200 mg daily). Virologic response criteria are stipulated for week 4 (≥ 0.5 log reduction), week 12 (≥ 1.0 log), and week 24 (≥ 2.0 log); patients who fail these criteria are designated treatment failures and discontinue. Results: ITT results for the 162 patients who have reached week 24, including dropouts and failures by

LOCF conventions: HCV RNA responses in the 2 higher-dose NM283+pegIFN comboRx arms are significantly greater vs pegIFN/RBV retreatment. By comparison to other Phase IIb data, early HCV RNA reductions are substantially greater in HCV-1 treatment-naïve patients with similar NM283/pegIFN regimens, confirming the difficulty in suppressing HCV in NR patients. No viral breakthrough has been seen to date. Conclusions: In non-responders to pegIFN/RBV, valopicitabine+pegIFN treatment at optimal dosing produces significantly greater HCV suppression compared to pegIFN/RBV retreatment, with antiviral efficacy proportional to valopicitabine dose. Continued treatment will determine if these encouraging viral responses at 24 weeks will result in viral clearance and SVR.

Treatment Group	Response at 24 Weeks		
	N	Mean ↓ HCV RNA (log ₁₀ IU/mL)	Median ↓ HCV (log ₁₀ IU/mL)
1 - PegIFN + RBV control	31	2.31	1.21
2- NM283 400 + pegIFN	40	2.49	2.31
3- NM283 400-800 ramp + pegIFN	38	3.01*	3.05
4- NM283 800 + pegIFN	32	3.32*	3.29
5- NM283 monoRx	21	0.54	0.42

* p<0.03 pooled 800+peg-IFN vs peg-IFN

226135: A Randomized Trial of Telbivudine (LdT) vs. Adefovir for HBeAg-Positive Chronic Hepatitis B: Results of the Primary Week 24 Analysis. *E. Jenny Heathcote, H L Chan, M Cho, C-L Lai, Y-M Moon, Y-C Chao, R Myers, G Minuk, P Marcellin, L Jeffers, W Sievert, R Kaiser, G Chao, N Brown, 018 Study Group*

Background: For optimizing patient management with the current antiviral armamentarium for hepatitis B, additional comparative studies are needed. Adefovir dipivoxil has significantly greater efficacy than placebo treatment but has not been evaluated in comparative trials. Telbivudine exhibited superior antiviral activity vs lamivudine in a large phase III trial, and those study results indicated that optimal viral suppression and clinical efficacy (ALT normalization, HBeAg loss/seroconversion) at 1 year were associated with maximal HBV DNA reductions in the first 6 months of treatment. Methods: This ongoing 1-year international trial is comparing the antiviral efficacy and safety of telbivudine vs adefovir. The enrolled ITT population is 133 adults with HBeAg-positive chronic hepatitis B. Key entry criteria were HBsAg+, HBeAg+, HBV DNA >6 log₁₀ copies/mL by COBAS Amplicor PCR assay, ALT 1.3-10 xULN, and compensated liver disease. Patients were randomized (2:1) to treatment with adefovir 10 mg/d or telbivudine 600 mg/d; at Week 24, half the adefovir cohort is secondarily randomized to switch to telbivudine. Completion of study treatment is at Week 52. The primary endpoint defined by the study protocol is HBV DNA reduction at Week 24, with secondary antiviral and clinical efficacy and safety endpoints assessed at Weeks 24 and 52. Results: Treatment groups were well-matched at baseline. Telbivudine was superior to adefovir on the primary efficacy endpoint (HBV DNA reduction at Week 24) and all other measures of direct antiviral efficacy (Table). ALT normalization was similar at Week 24. Both treatments have been well-tolerated to date. Conclusion: After 24 weeks, telbivudine exhibited significantly greater and more consistent antiviral efficacy than adefovir in HBeAg+ patients with chronic hepatitis B. One-year data, to be presented at the meeting, will assess the association of this difference in antiviral effect with subsequent clinical efficacy outcomes.

	N	Log ₁₀ HBV DNA ↓	% HBV DNA < 5 log ₁₀ †	% HBV DNA PCR-neg‡	% ALT normalized	% HBeAg loss
Telbivudine	44	6.37*	95%*	38.6%*	61.4%	16%
Adefovir	89	5.11	58%	12.4%	62.9%	10%

† percent of patients with HBV DNA level < 5 log₁₀ (AASLD & APASL guideline) ‡ COBAS PCR assay limit ≤300 copies/mL * p < 0.01, telbivudine vs. adefovir

226441: Comparison of Daily Consensus Interferon versus Peginterferon alfa 2a Extended Therapy of 72 Weeks for Peginterferon/Ribavirin Relapse Patients with Chronic Hepatitis C. *Kaiser S, Hass H, Lutze B, Gregor M*

Objective: Treatment with paginated interferon and RBV for 48 weeks in naive chronic Hepatitis C patients results in relapse rates of about 20-30%. Recently improved response rates have been observed in retreatment trials using an extended treatment duration of 72 weeks. Methods: The efficacy of CIFN daily dosing + RBV versus PEG IFN a2a + RBV for 72 weeks in patients with a prior relapse to 48 weeks of treatment with PEG IFN + RBV was evaluated. 81 patients have been included, with 83% having genotype 1. Average weight of patients was 78 kg. Patients were either treated with CIFN at 9 ug QD for 72 weeks or with PEG IFN a2a at 180 ug QW for 72 weeks, both in combination with weight-based RBV. Results: Data show that after the in initial 12 weeks a primary response with undetectable serum HCV-RNA was observed in 83% of patients in the

CIFN QD group and in 78% in the PEG IFN 180 ug group. At the end of treatment at week 72, a negative PCR was observed in 89% in the CIFN group, and in 76% of the PEG IFN 180 ug group (diff. not significant). The sustained viral response rates (SVR) were 69 and 44%, respectively ($p < 0.05$), indicating a significantly higher relapse rate in patients treated with PEG IFN a2a. No growth factors were used in this study. Three patients experienced grade III thrombocytopenias, while no grade IV neutropenias or thrombocytopenias were observed. The overall tolerability of the CIFN QD regimen was comparable to the PEG IFN a2a therapy, while the CIFN QD regimen lead to a higher rate of injection site reactions and a slightly higher drop out rate of 18% versus 12% for the PEG IFN a2a group. In contrast, hematologic grade III alterations were higher in the PEG IFN a2a group. Conclusions: Extended CIFN daily dosing combination therapy for 72 weeks shows promising response rates in comparison to PEG IFN a2a combination therapy in previous relapse patients to standard PEG IFN/RBV therapy. The data are especially interesting since most patients were genotype I relapsers. Although a significant proportion of patients experienced a second relapse after cessation of therapy, the overall sustained response rates are nevertheless promising showing a SVR in up to 70% of patients. It is concluded that extended treatment with CIFN in combination with RBV may be an effective treatment modality for this difficult-to-treat patient group.

226585: Higher Susceptibility of Peginterferon alfa 2a versus Peginterferon alfa 2b Nonresponder Patients with Chronic Hepatitis C to Retreatment with Consensus Interferon Daily Dosing and Ribavirin. Kaiser S, Hass H, Lutze B, Gregor M

Objective: Current standard treatment with pegylated interferon I (PEG IFN) and ribavirin (RBV) in genotype 1 patients shows sustained response rates of 31 – 47%, thus leaving more than half of the patients with a relapse or nonresponse to. Recently improved response rates have been observed in pilot trials using consensus interferon (CIFN) in combination therapy in PEG IFN/RBV nonresponders. Methods: The efficacy of CIFN daily dosing and induction therapy followed by CIFN/RBV in PEG IFN combination treatment nonresponders was evaluated. 95 patients have been included, with 9% having genotype 1. Average weight of patients was 76 kg. Patients were either treated with CIFN at 9 ug QD for 16 weeks or with CIFN 27 ug QD for 4 weeks, followed by 12 weeks of CIFN 18 ug QD. Thereafter, treatment was continued in all treatment groups with CIFN at 9 ug QD with weight-based RBV for 32-56 weeks, depending when a patient became first PCR negative, ensuring a treatment period for 48 weeks with a negative PCR. Results: Data show that after the initial 12 weeks of CIFN monotherapy, a primary response with undetectable serum HCV-RNA was observed in 35% of patients with a prior nonresponse to PEG IFN a2b and in 51% in prior PEG IFN a2a nonresponders. At the end of treatment, a negative PCR was observed in 37% in PEG IFN a2b nonresponders, and in 51% of PEG IFN a2a nonresponders. The sustained viral response rates (SVR) were 21% and 38% for PEG IFN a2b and PEG a2a nonresponders respectively. When response rates were calculated according to the treatment arm used, the SVR for PEG IFN a2b nonresponders were 18% in the CIFN 9 ug arm and 25% in the CIFN high dose arm. For PEG IFN a2a nonresponders, the SVR were 34% and 41% for the CIFN 9 ug dose and high dose arms, respectively. The overall tolerability of the CIFN 9 ug regimen was comparable to a standard therapy with pegylated IFN and RBV, while the CIFN 27/18/9 ug regimen was less tolerable during the high dose induction period. However, drop out rates were not different between the two dosing regimen. Conclusions: CIFN daily dosing/induction therapy together with subsequent RBV combination therapy thus shows promising response rates in previous PEG IFN combination therapy non-responders. Especially PEG IFN a2a nonresponders appear to have a benefit from CIFN QD retreatment. It is concluded that CIFN may be an effective treatment modality for this difficult-to-treat patient group.