

Report from Digestive Diseases Week, Atlanta, GA: May 19-23, 2001

by: *Patty Perkins & Alan Franciscus*

Digestive Diseases Week (DDW) is the second largest US meeting on diseases of the GI tract, including the liver. DDW attracts over 14,000 conferees from around the globe, including basic and clinical scientists, medical providers, and industry experts including manufacturers of pharmaceuticals, devices, assays, and nutritional products.

DAY 1

After arriving in Atlanta on Saturday afternoon during an intense thunder and lightning storm, today Atlanta weather is cloudy and humid, with light rain and jasmine-scented breezes to cool off that stickiness. Conference locale is next to the CNN Center. So far we have had no Ted Turner sightings. Your correspondents are trying to beat the heat and avoid those pecans!!

Unfortunately, today's focus is minimal on hepatitis C, but both oral and poster presentations include: basic science of hepatitis B, GI cancer, irritable bowel syndrome and Crohn's Disease, ulcerative colitis, and HCV pathogenesis (cellular activity and damage caused by HCV).

HCV PATHOGENESIS

In a session co-chaired by Drs. John Vierling and Teresa Wright (Cedars Sinai, Los Angeles and UCSF/VAMC, SF, respectively), sessions showcased host virus immune response and potential genetic markers for HCV viral clearance. Groups in Germany and collaboration between teams in Italy and New Orleans offered the two sessions of most immediate clinical relevance.

The first of these presentations, presented by Dr. Susanne Ross and German colleagues, assessed genetic predictors of spontaneous viral elimination of HCV. Noting that spontaneous viral clearance of HCV is clinically rare, this team sought to determine the influence of genetic variations of the immunomodulatory (regulate and calms immune system) genes on the course of HCV infection in relation to: spontaneous recovery, chronic hepatitis and cirrhosis. The team analyzed genetic markers from 257 HCV+ Caucasian patients in Northern Germany, 86% with Genotype 1, and then evaluated the frequency of genetic mutations. The group identified two genetic variants that predicted the **inability** to eliminate HCV: the rare allele (T at position 880 in the IL1-alpha promoter and the rare allele (Ile) at amino acid position 64 of the CCR2 gene. CCR2, a chemokine receptor, has long been studied in HIV immunomodulatory therapy and may be a likely candidate for further drug development study. Limitations of this analysis include: only Caucasians studied (this area of Germany is predominantly Caucasian), and only Genotype 1 data was analyzed. Additional research in other areas of Germany is underway.

An additional session potentially relevant to drug development was presented by Dr. Roberto Burioni from Ancona, Italy in collaboration with basic science researchers at Tulane University in New Orleans. The non-structural protein, NS3 is on the surface of the HCV molecule, and 3 key enzymes—protease, helicase, and nucleoside triphosphatase (NTPase)—seem likely targets for investigation. In this study, the researchers increased the NS3 gene activity through molecular biology techniques, creating a human monoclonal antibody and then studied the ability of this antibody, known as **Fab**, to inhibit the helicase activity of NS3.

Preliminary evidence indicated a decrease in measurable level of negative-stranded HCV-RNA from this **anti-NS3-Fab complex**, suggesting inhibition of helicase activity. This would argue for a new strategy of intracellular immunization and a potential new drug therapy strategy for HCV.

CONCLUSION

The Exhibit Area is like a gastrointestinal carnival complete with huge complaining stomachs, inflamed esophagi (plural for esophagus), and authentic fire engines to put out the heartburn BURN!! Your mild mannered reporters have a simple but elegant table that features information on HCV in English and

Spanish, but unfortunately we can't have a talking liver. Donations towards the purchase of aforementioned talking liver will be graciously accepted but likely spent on much needed patient advocacy.

Monday's program features more clinical science on all aspects of hepatitis C, results of trials on PEGASYS™, ribavirin, and amantadine; treatment issues for mentally ill or methadone maintained patients; comparisons of PEGASYS™ after discontinuation from REBETRON™; treatment adherence issues for incarcerated African American men; and latest findings on living donor liver transplants.

DAY 2

Another enjoyable but warm and humid day in Atlanta, GA. Now we know what is meant by Southern hospitality! The people here are warm, friendly, and very helpful and go out of their way to help these poor lost Northerners (though PP was born in Virginia). We could really entertain living here if it wasn't for that humidity!

Monday included some standing-room-only symposia, more presentations and posters. Lots and lots of conferees and it sometimes took 20 minutes just to get into the Exhibit Area! Both of us are so overloaded with data we think our heads may explode. Hopefully, we will be able to retain some of the data presented.

Here is a review of some of the most interesting presentations.

SELECTING THE LIVER TRANSPLANT RECIPIENT: WHEN TO REFER

This standing room only session was made up of 20% liver transplant surgeons and staff and 80% hepatologists, GI's, or other clinicians. The key speaker was Dr. Robert Carithers, from the University of Washington, Seattle, and Chief of its Medical Transplantation Service. This was an organized and thoughtful presentation, explaining pros/cons of the current organ procurement and listing system for adults in the US. As our readers know from previous **HCV Advocate** reports, the current system is fraught with conflict, inequity, long waiting lists, and great regional disparity in organ access. At the urging of both the federal DHHS and the Institute of Medicine, a joint expert panel from both the Society of Liver Transplant Surgeons and the American Association for the Advancement of Liver Disease was convened in 1997 and recently issued guidelines for re-design of the current liver transplant referral system. These recommendations are now out for public comment until August 1, 2001. The key proposed changes of note here is a new scoring system called the Model for End Stage Liver Disease or "MELD," designed to replace some of the subjectivity of the current scoring system. These new guidelines are designed to decrease the likelihood of physicians admitting their patients to the hospital or the Surgical Intensive Care Unit (ICU) in order to advance their standing for a liver, or the continuing conflict of having priority only given to the sickest patients first. Preliminary data suggests that the new MELD system correlates well with at least 3-month and 1-year mortality data, meaning the higher the score the lower the 3-month and 1-yr. mortality. Two other sessions scheduled for this morning, 5/22/01, will present data refuting some of these preliminary assumptions. An animated Q & A followed this section, with discussions on listing of co-infected patients, handling alcohol relapse pre/post transplant.

TREATMENT OF CHRONIC HEPATITIS C (HCV) IN THE INMATE SETTING: DOES COMPLIANCE AFFECT RESPONSE IN AFRICAN AMERICANS?

Dr. Richard Sterling of the Virginia Commonwealth University in Richmond presented this poster session, with the study designed to explore the efficacy of treating HCV in the prison population. This was an open-label retrospective study.

At this prison, all prisoners were offered HCV testing. Inmates testing HCV-RNA positive were offered biopsy, and those with scores of 5 or greater on HAI (histologic activity index), no other serious medical conditions such as HIV and HBV, or complications from liver disease. To date, 60 inmates have been treated with combination therapy (INFa-2b (interferon 3 mu 3 tiw) and RVN-ribavirin (1000-1200 mg/d) given under direct supervision. Approximately 45% were African Americans, 22% high viral loads, 75% genotype

1, and a large proportion had advanced liver disease. 58 of the 60 treated patients cleared the virus sometime during treatment, with 35 end-of-treatment responders. Follow-up data: 8 achieved sustained response, 3 relapsed, and 13 still on treatment or at end of treatment responded and are in follow-up phase. 11 prisoners were lost to follow-up from parole, transfer or missed medical appointments. More data to follow at 6-months post treatment and likely will be presented at the November 2001 AASLD meeting in Dallas.

The authors of this poster concluded: "This study demonstrates that treatment of HCV in the inmate population is both feasible and has similar rate of virologic response as that previously reported. The comparable rates of virologic response in both AA and Caucasians at least while on treatment strongly suggests that both compliance and the use of RVN along with INF are necessary to enhance virologic response in AA with HCV."

Treatment of Chronic Hepatitis C with Interferon-Alpha-2a and Ribavirin in Patients with a Psychiatric History, Earlier Drug Addiction or Methadone Substitution Compared to Controls: A Prospective Controlled Study

Martin Schaeffer, MD and colleagues from Munich, Germany presented a well-designed paper on treatment issues for two other so-called "difficult" populations. Your correspondent (PP) was only able to hear the conclusions and Q & A. Key findings from this study revealed that only not-in-drug treatment drug users had high drop out rates, and that a carefully designed interdisciplinary program between infectious disease, GI, nursing, and psychiatry aided in patient adherence and reductions in drop-outs due to psychiatric side effects. Another lively Q & A ensued with some questioners arguing that anyone with any thought of suicide at baseline or any mental health indication should be excluded from combination therapy—period. The moderator of this paper made one of the most telling comments, suggesting that the ongoing debate about whether hepatologists or infectious disease physicians should provide HCV treatment to the so-called "difficult" patient populations has been answered: psychiatrists are really the best medical providers for this group. For regular **HCV Advocate** readers, Dr. Diana Sylvestre, who wrote an article on HCV treatment for methadone patients, and your correspondent (PP) have a poster on Tuesday, May 22, on HCV treatment of methadone patients, which confirms many of this paper's findings.

ENHANCING COMMUNICATION SKILLS IN GASTROENTEROLOGY: AN INTERACTIVE WORKSHOP BY GARY A. GLOBER, MD

This late afternoon session was held to help physicians learn better communication skills with their patients. A variety of issues were discussed that promoted better doctor/patient communication. Topics included: breaking bad news, being honest with patients but not taking away hope, among other areas. The physicians in attendance were given exercises to help with the entire process of dealing with the emotional issues of patient care.

As a patient your correspondent (AF) was extremely excited to see this workshop offered. It would be great if this type of course were offered/required of all physicians every few years, perhaps to maintain board certification or accreditation. While there are many, many physicians that can successfully care for a patient's physicals and emotional health, we hope that future workshops on this issue will be better attended.

DAY 3

Another beautiful day in Atlanta, GA, and a big afternoon rainstorm promised sunshine and cooler temperatures. Your correspondents found this a pleasant relief from the hot and humid weather of the past few days. Yesterday, lots of information was presented on hepatitis C. A brief summary follows below. More clinical data reports will be discussed in the **HCV Advocate** in the coming months.

MELD SCORING SYSTEM NOT PREDICTIVE OF MORTALITY IN PATIENTS WAITING FOR LIVER TRANSPLANTATION

Dr. Tim McCashland presented a report from the University of Nebraska Medical Center, suggesting that in a

real-life liver transplant environment the Model for End Stage Liver Disease or MELD may not accurately predict long-term mortality in liver transplant patients. In this analysis, MELD successfully separated patients into low and high-risk groups. Over a one-year period, 8 of 61 patients died in the low risk group and 8/9 died in the high-risk group. In this analysis, MELD underestimated mortality in the high-risk group and overestimated it in the low risk. The author stated: “The model was set up to calculate mortality for three months, but a lot of patients wait [for a liver transplant] for two years... There’s still a big spread on what the model predicts and what actually happened with our patients.” He concluded that other studies from larger transplant centers might be helpful in answering these issues.

ONCE WEEKLY RECOMBINANT HUMAN ERYTHROPOETIN (EPOETIN ALPHA) FACILITATES OPTIMAL RIBAVIRIN (RBV) DOSING IN HCV-INFECTED PATIENTS RECEIVING INTERFERON-A-2B (IFN)/RBV COMBINATION THERAPY

Dr. Dieterich presented this paper from New York City in a morning session and additional aspects were presented in a pharma-sponsored evening program by Drs. Dieterich and Sulkowski (Johns Hopkins, Baltimore). This same team is currently conducting a comparable study in co-infected patients. Since the hemolytic anemia often induced by RBV has been a major problem for many patients, often requiring RBV dose reduction and impacting sustained viral response (SVR), this is an important new treatment and avenue for investigation. The primary conclusion in this open-label randomized multi-center study suggested that a weekly high dose (40,000 units) of Epoetin-Alpha was well tolerated and increased hemoglobin levels in HCV positive patients on standard combination therapy. Epoetin-Alpha increased the percentage of patients receiving RBV doses > 10.6/mg/kg/day, suggested as the minimum dose to increase sustained viral response. In the Q&A session, two investigators brought up the very real cost considerations of this treatment, in the New York and Baltimore settings, as high as \$400/week (many patients are on therapy for 6 months), in some cases close to doubling the cost of combination therapy, a very real issue in a managed care environment. Prices may come down as drug come off patent or Epoetin precursors come on the market.

SCHERING-PLOUGH REPORTS INTERIM RESULTS OF PEG-INTRON™ PLUS REBETOL™ CLINICAL TRIAL

Schering-Plough reported preliminary data from 24 weeks of therapy with combination of PEG-INTRON and REBETOL. In a study led by Ira M. Jacobson, M.D., chief, division of gastroenterology and hepatology, Weill Medical College of Cornell University, New York reported that people that did not respond to previous combination therapy achieved a 35% virologic response. Interpreting these results is problematic since no data was given on dosage, genotype, age, viral load and/or severity of disease. A word of caution – these are only 24-week results, but this trial may show promise for the difficult to treat non-responder.

Source: Schering-Plough

SCHEARWATER ANNOUNCES LATEST CLINICAL TRIAL DATA FOR INVESTIGATIONAL HEPATITIS C TREATMENT – PEGASYS®

Results from a clinical trial that directly compared the efficacy and safety of Pegasys compared with Rebetron™ (interferon alfa-2b plus ribavirin) were released on May 22, 2001 at DDW.

This study included more than 1,100 treatment-naïve (not previously treated) patients with hepatitis C. Patients were treated for 48 weeks and followed-up for an additional 24 weeks. The population in this study consisted of patients with genotype 1 – 65%, and compensated cirrhosis – 14%.

| Treatment Arm | No. Patients | SVR* |
|---|--------------|------|
| 1.Pegasys (180 mcg) plus ribavirin (1000 or 1200g) | 453 | 56% |
| 2.Rebetron (interferon 3 MIU plus ribavirin (1000 or 1200 mg) | 444 | 45% |
| 3.Pegasys (180 mcg) plus placebo | 224 | 30% |

Patients treated with Pegasys plus ribavirin infected with genotype 1 achieved 46% SVR compared to 37% for patients treated with Rebetron (interferon 3 MIU plus ribavirin (1000-1200 mg)

These results are encouraging because the patients in this study with genotype 1 and compensated cirrhosis are considered more difficult to treat

Source: Shearwater Corporation

Outcome of Liver Transplantation in Patients with Diabetes Mellitus: A Case Control Study

An additional topic of interest included long-term morbidity & mortality data among diabetic liver transplant patients followed at Johns Hopkins School of Medicine in Baltimore. In both poster and oral presentations, Drs. Thulavuth & John presented both clinical findings (poster) and data from a case control study (oral presentation) of long-term morbidity and mortality in patients who were diabetic prior to liver transplantation, with 1/3 of these patients African-American. While there was a trend to better mortality among diabetics as compared to non-diabetics in Years 1 & 2 post-transplant, by Years 3-5, diabetics experienced statistically greater likelihood of the following complications: cardiovascular problems; major and minor infections; kidney, bladder, and eye problems; and additional GI problems, including other GI cancers. The authors recommended considering additional evaluations in diabetic transplant patients—including more intensive cardiovascular and eye exams, and better and more frequent measures of glucose levels. Since diabetes is a major public health problem among Latinos, look for future similar studies in Latino populations from Miami, Texas, and Los Angeles transplant centers.

Conclusion

This will wrap up the conference coverage for DDW. Look for more information on the information presented here in the coming months. This was an extremely well run and organized conference and we would like to thank the conference organizers as well as the people in the press room for all their help and support.