

Hepatitis C Conference Links

Highlights of AASLD Postgraduate Course

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An excellent course was presented at the recent American Association for the Study of Liver Disease Conference held in Dallas, Texas on viral hepatitis, which included all types of hepatitis with epidemiology, virology, clinical, and therapy combined.

Hepatitis B Vaccination

Dr. Miriam Alter presented data on hepatitis B vaccination. In a study of Alaskan Natives, 25 -50% of non-responders responded to one additional dose of hepatitis B vaccination and 40-50% responded after three more doses. There was no added benefit in additional vaccination. In immunocompetent patients, immunity lasted 10-15 years even though anti-HBs was lost in 10-50% of patients, there was no disease noted. In immunocompromised patients, it is unclear how long immunity lasts and there is some discussion of whether a booster should be given when anti-HBs falls below 10 I.U. per ml. Pre-S vaccinations that include larger surface proteins have been shown to have a higher response: 60% response in those who have previously not responded to recombinant vaccinations.

Natural History of Hepatitis C

Excellent data were presented on the natural history of hepatitis C. This is a new and emerging area showing that hepatitis C disease may be much less severe than previously thought. Data from Ireland by Dr Kenny Walsh reported on pregnant women who had received Rhogam for treatment of Rh-incompatibility. Genotype 1 subjects were studied 17 years after infection and only 2% of patients had cirrhosis. Dr Vogt studied 458 German children (New England Journal of Medicine) 20 years after infection. This study found that 45% of the patients had recovered and lost RNA and only 0.3% had cirrhosis. Dr Leonard Seeff followed patients 23 years after acquisition of hepatitis C. There was no difference in all cause mortality (death rate) between the 500 patients who have had hepatitis C and 1000 case controls. Of this group, liver related deaths were higher in the hepatitis C group at 3.1% compared to 1.3% in case controls and 56% of these patients died - 2% of liver disease. Most patients died of causes related to their need for transfusion. This brings up the question: "Is the natural history of hepatitis C through transfusion with a large amount of virus worse than that by acquisition through other parenteral routes?"

Drs Seeff and Alter discussed an algorithm suggesting that after acute infection at least 20% of individuals recovered (cleared the virus). Eighty percent developed persistent infection of whom 1/3 have stable chronic hepatitis, 1/3 have severe progression, and 1/3 have variable progression. This lead to an overall favorable outcome in 2/3 of patients and 1/3 of patients having on-going progressive disease. In prospective studies, after 10-20 years of exposure the incidence of cirrhosis was 7-15%. In cohort studies, 17-45 years from exposure the incidence of cirrhosis was 0.3-21%. This is much lower than previously thought.

The following papers were reviewed. Dr David Thomas' study from JAMA of 1667 patients who were HCV antibody positive were followed for 8-years. 2.4% had end-stage liver disease. 374 people died of non-liver related problems, and 22.4% had liver damage related to alcohol. He biopsied 210 patients, two of whom had cirrhosis. Dr. Rogers' study described (Hepatology 2000) 95 patients from Australia who acquired hepatitis C between 1971 and 1975. Twenty years later 6% were PCR negative, only 51% were PCR positive and four of those 51% had cirrhosis. No individuals had hepatocellular carcinoma.

The rates of spontaneous recovery (cleared the virus) varied. In transfusion related HCV adults studied by Dr Seeff the spontaneous recovery rate was 24%; in the NHANES 3 Study by Dr Alter 26%; In leukemic children by Dr Losasciulli, 29%; in the Irish Rhogam Study 45%, and the transfusion related HCV study in children in Germany, the rate was 45%. Lessons from these studies are that 1) there is a higher spontaneous recovery than previously thought; 2) there is a favorable outcome in 64% of patients who develop hepatitis C with either recovery or stable benign disease; 3) there is a severe outcome in less than 1/3 of patients who develop progressive disease of whom somewhere between 7-15% develop cirrhosis.

Chronic Liver Disease and Viral Hepatitis in the United States

Dr Norah Terrault presented data on chronic liver disease and viral hepatitis in the U.S. Chronic liver disease is the 10th most common cause of death in the USA. In patients with chronic hepatitis C infection, 65% occurs in ages 30-39 years. Dr Victor Navarro looked at a GI community practice in the Northeast and found that 52% of patients with chronic liver disease had hepatitis C with or without alcohol use. Review of a large managed care group in California, abnormal Liver Function Tests (LFT) for longer than 6 months was the definition of chronic liver disease and it occurred in 72 patients per 100,000 case subjects. Forty-seven of these 72 patients were seen by gastroenterologists, but the rest were not referred to liver specialists. It was unclear whether they did not have liver disease or were not deemed suitable patients for therapy.

Interferon and Ribavirin Treatment- Achieving Optimal Dose Response

Dr John McHutchison presented data on interferon and ribavirin therapy. His group reviewed the optimal dose of ribavirin necessary to aid in the interferon's anti-viral effect. He showed data from Schering that ribavirin at 400 mg dose led to a 1.6 log decrease in serum HCV RNA. A ribavirin dose of 600mg led to 1.7 log decrease in HCV RNA, ribavirin at 800mg/ day led to 2.09 decrease in HCV RNA with 1000mg ribavirin to 2.22 log decrease in HCV RNA. Thus, ribavirin at doses under 800mg causes less anemia but is less effective.

Re-treatment of Non-Responders in HCV

Dr Jenny Heathcote reviewed re-treatment of non-responders. She found that re-treatment of those who had initially responded to therapy and then relapsed resulted in a 10-70% response rate with 6 or 12 months of interferon treatment. However, this was not seen in non-responders to IFN. Regardless of the dose, the length of interferon re-treatment of non-responders up to 12 months lead to less than 10% sustained virologic response in the majority of patients. Genotype 2 or 3 patients had a 22% response in data reported by Dr. Solko Schalm.

Pegylated Interferon and Ribavirin

Dr Michael Manns presented the sustained virologic response of 1530 patients treated with 12 kg pegylated interferon (Peg-Intron) and ribavirin. Sixty-five percent of the patients were male, 68% had genotype 1, 69% had HCV RNA >2,000,000 copies per ml and 10% of the patients were cirrhotic. The overall response to 48 weeks of interferon was reviewed for standard therapy with interferon alpha-2B ((Intron A) plus ribavirin or pegylated IFN low dose (that is, 0.5 µg/kg) or high dose (1.5µg/kg of pegylated interferon) plus ribavirin. In all patients, the results were 54% for all groups: genotype-1 patients had a 33% response to standard ribavirin and a 42% response to high dose pegylated IFN. In genotype 2 or 3, 80% of patients responded. He then showed data comparing ribavirin dose and interferon dose per kilogram of body weight. They found that those weighing less than 65kg had a 57% response with a fixed dose of interferon, 47% with a fixed dose of ribavirin, and a 62% response when both interferon and ribavirin were adjusted to body weight. Those weighing 65-85 kg showed 48% response to fixed interferon, 49% response to fixed ribavirin and a 55% response when both interferon and ribavirin were adjusted to body weight. In patients weighing greater than 65kg, the responses were overall lower with a 41% response to fixed interferon, 46% response to fixed ribavirin, and a 49% response when both ribavirin and interferon were adjusted for body weight. The incidence of side effects were slightly higher in the high dose pegylated interferon, with neutropenia (low

white blood cells) double that of standard interferon.

Pegylated Interferon and Improved Liver Histology

Dr. Jenny Heathcote looked at histologic response to 40KD pegylated interferon (Pegasys) and compared it with standard interferon. The overall histologic response in pegylated IFN was 57% compared to 41% noted in those receiving standard IFN. In those with sustained virologic response, the histologic response was seen in 83% versus 79%. In virologic non-responders, histologic improvements were noted in 44% of patients receiving pegylated IFN and 36% of those receiving interferon 2A. Histological improvement was assessed by greater than 2 HAI units on the Knodell score.

Response to Therapy for Patients with Normal ALT's

The effect of response to therapy and normal alanine aminotransferases (ALT's) were studied by Dr Estaban. 249 patients were followed for over 8 years and had two liver biopsies 4 years apart. He compared those with normal ALT's and those with abnormal ALT's and found a higher percentage of females in the normal ALT's (71%) compared to abnormal ALT's (47%). Any alcohol intake was noted in 21% of those with normal ALT's and 40% of those with abnormal ALT's. Heavy alcohol use greater than 50g/day occurred in 6% of those with normal ALT and 17% of those with abnormal ALT. Liver biopsies differed between those with normal and abnormal ALT. In those with normal ALT, 64% were mild, 34% were moderate and 2% severe. In those with abnormal ALT, 34% had mild biopsies, 64% moderate and 20% severe. Four years later, a repeat biopsy in normal ALT patients showed no cirrhosis, decompensation, hepatocellular carcinoma or death. In 114 patients with abnormal ALT, 8% had progressed to cirrhosis, 2% decompensated, 2% had hepatocellular carcinoma and 2% had died.

HIV / HCV Co-infection

De Martino from France studied 299 patients of whom 50 were co-infected with HIV and HCV. Patients were followed over 28 months. The three year survival was 47% in HIV positive/ HCV positive and 72% in HIV negative / HCV positive patients. Fifty-six percent of HIV positive patients and HCV positive patients decompensated compared to 19% of HIVnegative / HCV positive patients. Twenty-nine percent of HIV positive patients had ascites whereas 10% of HIV negative did. Variceal bleeds and portal systemic encephalopathy occurred in 20% and 9% of HIV + compared to 4% of HIV negative / HCV positive patients. Analysis revealed that HIV positive and HCV positive patients were younger at the time of diagnosis. There were more males, more history of injection drug use, a higher alcohol intake, and prothrombin time. One-third of the patients had CD4 counts less than 200. There was no difference in virologic markers, metavir score, Childs Pugh score or biochemistry. In multivariate analysis, the relative risk of HIV was 3.4 and of alcohol>50g/day, 2.3.

Thus, these snapshots from AASLD showed that there are new therapies available, that fibrosis can be reversed to some extent with therapy, and that the natural history of the disease is less severe than previously thought.