KY Hepatitis Connections

Greetings partners and colleagues! March is here and spring is right around the corner. I have settled into my new role and have received input from many of you related to the obstacles and barriers for treatment of hepatitis C virus (HCV) infected patients in our local communities.

Now more than ever do I believe it is imperative for our program to create a legacy of working with partners and colleagues across the Commonwealth of Kentucky to prevent the transmission of viral hepatitis, particularly viral hepatitis caused by hepatitis A virus hepatitis B virus, and hepatitis C virus. Our team has created a Web-based survey to determine adult hepatitis prevention needs, most particularly related to Hepatitis B and Hepatitis C. http://www.surveymonkey.com/s/KY2013viralhepatitissurvey

Your input is of most value as we move forward to determine the needs for the prevention and treatment of individuals with hepatitis throughout the Commonwealth of KY. Please click on the above link and complete the Survey by March 20, 2013. Your knowledge and continued input are greatly valued, as we are committed to keeping you up to date on shared progress in the medical community on viral hepatitis and its impact on families throughout the Commonwealth. Follow us on Facebook: KY Viral Hepatitis.

Kathy Sanders, RN MSN
Adult Viral Hepatitis Prevention Program Manager
Kentucky Department for Public Health

"Triple Trouble: Infection with Hepatitis B Increases Risk of Death for People with HIV and Hepatitis C Co-infection"

AIDSMAP (02.19.13):: Michael Carter
http://www.aidsmap.com/Triple-trouble-infection-with-hepatitis-B-increases-risk-of-death-for-people-with-HIV-and-hepatitis-C-co-infection/page/2571222/

A Spanish research team reports that hepatitis B infection increases the risk of death by 75 percent for HIV/ hepatitis C-co-infected people. Earlier studies have focused on HIV/ hepatitis C co-infection or HIV/hepatitis B co-infection, but not the consequences of co-infection with all three viruses. Transmission is similar for HIV, hepatitis B, and hepatitis C.

The study analyzed data from the VACH cohort, comprised of 6,342 HIV/hepatitis C-infected individuals. Six percent of the VACH cohort also had hepatitis B. Study participants who had all three viruses were likely to be older, male, have a lower CD4 count, and higher AST-to-platelet index than cohort members co-infected only with HIV and hepatitis C.

VACH data provided almost 26,000 person-years of follow-up with a total of 543 deaths and an average mortality rate of 2.1 per 100 person years. In contrast, co-infection with all three viruses increased the mortality rate per 100 person years to 3.78. Researchers initially concluded that co-infection with hepatitis B increased the mortality rate by 90 percent, but they revised their estimate to 75 percent when they factored in AIDS-defining illness, age, HIV and hepatitis C treatment, CD4 cell count, and viral load. Factors that increased mortality risk for HIV/hepatitis B/hepatitis C co-infected people included “detectable” viral load and older age. Higher CD4 cell count, HIV treatment, and tenofovir treatment regimen (effective against HIV, hepatitis B, and hepatitis C) comprised factors associated with a better outcome.

The study also indicated that HIV/hepatitis B/hepatitis C co-infection increases the risk of liver disease-related death. Researchers strongly recommended hepatitis B immunization for HIV-infected people and people at risk of HIV infection.

The full article, “Hepatitis B Virus Infection Predicts Mortality of HIV and Hepatitis C Virus Co-infected Patients” was published online in the journal AIDS..

Vitamin A deficiency reduced response to therapy for chronic HCV

Bitetto D. *Hepatology*. 2013; http://onlinelibrary.wiley.com/doi/10.1002/hep.26186/abstract.

- February 14, 2013

Vitamin A deficiency is common among patients with chronic hepatitis C, and is associated with nonresponse to interferon-based treatment, according to recent results.

Researchers measured vitamin A and 25-OH vitamin D levels in 199 treatment-naive patients with chronic HCV before receiving interferon (INF)-based treatment, and compared them with 119 healthy controls. Participants also underwent genotyping for the IL-28B rs12979860 C>T polymorphism.

Patients with HCV had lower vitamin A serum levels than controls (256 ng/mL vs. 742 ng/mL; *P*<.0001). Vitamin A deficiency (200 ng/mL or less) was observed in 42.2% of patients, while 19.6% had severe vitamin A deficiency (100 ng/mL or less). Vitamin D deficiency (20 ng/mL or less) was present in 45.8% of evaluable patients; 9% were vitamin D deficient and severely vitamin A deficient.

Sustained viral response (SVR) occurred in 84.4% of genotype 2 or 3 patients and 42.2% of those with genotypes 1, 4 or 5. Nonresponse occurred in 21.6% of evaluable patients, including 2.3% of those with genotypes 2 or 3 and 37.5% of those with the more difficult-to-treat HCV genotypes. More people with severe vitamin A deficiency experienced nonresponse to treatment, overall (36.1% of cases vs. 18.2%; *P*=.019) and particularly among those with difficult-to-treat genotypes (61.9% vs. 31% of nondeficient participants; *P*=.015).

Multivariate analysis indicated associations between treatment nonresponse and vitamin A levels of 100 ng/mL or less (OR=3.68, 1.03-13.2); HCV RNA above 600,000 IU/mL (OR=4.87, 1.48-16.0); IL-28B T/* genotype (OR=22.8, 3.92-13.3); baseline gamma-glutamyl transpeptidase levels above 60 IU/mL (6.33, 1.92-20.8), and a cumulative ribavirin dose of 80% or lower (3.89, 1.05-14.4) for difficult-to-treat patients (95% CI for all).

“The real novelty and probably the most important finding … is the association between serum vitamin A deficiency and the condition of nonresponse to antiviral therapy, suggesting that vitamin A could be an important and modifiable factor interfering with IFN sensitivity in patients with chronic hepatitis C,” the researchers wrote. “ … vitamin A supplementation and normalization of its serum levels, before antiviral treatment, could enhance the responsiveness to IFN-based antiviral therapy.”

Durability of a sustained virological response, late clinical sequelae, and long-term changes in aspartate aminotransferase to the platelet ratio index after successful treatment with peginterferon/ribavirin for chronic hepatitis C: a prospective study.

Papastergiou V, Stampori M, Lisgos P, Pselas C, Prodromidou K, Karatapanis S.
Source: http://www.ncbi.nlm.nih.gov/pubmed/23395996

Liver Clinic, First Department of Internal Medicine, General Hospital of Rhodes, Rhodes, Greece.

Abstract

OBJECTIVES: Previous studies, mostly retrospective using conventional interferon, have suggested a favorable prognosis for patients with chronic hepatitis C and a sustained virological response (SVR). However, long-term outcome, including changes in the degree of hepatic fibrosis, of SVR patients in the era of pegylated interferon (PegIFN) remains underdefined. We prospectively evaluated the long-term virological, clinical, and biochemical outcomes, including aspartate aminotransferase-to-platelet ratio index (APRI), in chronic hepatitis C patients with an SVR.

PATIENTS AND METHODS: We included 145 consecutive, treatment-naive chronic hepatitis C patients (mean age 47.3±9.1 years; 87 men; 42.1% genotype 1; 36.6% genotype 2/3) who achieved an SVR after combination therapy with PegIFN-α/ribavirin.

RESULTS: The mean follow-up time was 68.8±35 months. The overall incidence of hepatocellular carcinoma (HCC) and liver-related death was 1.4 and 0.7%, respectively. Among nine (7.6%) patients with pretreatment cirrhosis, two (22.2%) developed HCC and one of them (11.1%) died. No patient had conclusive evidence of late virological relapse. All patients retained normal liver biochemistry, except for five of 145 (3.5%), who had persistently elevated transaminase levels, all of whom were diagnosed with new liver disease. APRI values improved significantly with treatment (0.95±1.09 vs. 0.66±0.64, P<0.001) and continued to improve after a mean of 61.4±45.5 months from an SVR in patients (n=54; 37.2%) with significant (Metavir ≥F2) pretreatment fibrosis (1.13±0.66 vs. 0.67±0.45, P<0.001).

CONCLUSION: The long-term outcome, including APRI, of chronic hepatitis C patients treated successfully with PegIFN/ribavirin and followed for a mean of 5.7 years is favorable. However, a high risk of progression to HCC and liver-related death remains for patients with pretreatment cirrhosis, in our setting, as high as 22.2 and 11.1%, respectively.

An Epidemiologic Update on Hepatitis C Infection in Persons Living With or at Risk of HIV Infection

J Infect Dis. 2013 Mar;207 Suppl 1:S1-6. http://www.ncbi.nlm.nih.gov/pubmed/23390299 .
Kim AY, Onofrey S, Church DR.
Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Abstract

Due to shared routes of transmission, co-infection with both human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) is relatively common and results in accelerated liver disease, driving morbidity and mortality. Deaths related to HCV now exceed deaths related to HIV in the United States, and co-infected patients bear a significant proportion of that mortality. This burden may be addressed by novel antiviral therapies that promise increased rates of cure or by enhanced access to liver transplantation, but these are costly interventions. Ultimately, the future burden of co-infection is addressed by greater understanding of who is at risk for development of each infection, thus guiding preventive efforts. Key recent reports regarding the US burden of morbidity and mortality due to HCV and groups at risk for co-infection are reviewed, with a focus on recently described HCV occurring among young injection drug users and men who have sex with men. Given the lack of available vaccine against HCV, enhanced detection and surveillance is a vital component of our public health strategy to combat HCV. The entire article is available at: http://jid.oxfordjournals.org/content/207/suppl_1/S1.full.pdf+html?sid=964a1486-2619-4974-8164-49934b0bd387

The Sanford Guide introduces an app for Hepatitis treatment

Hepatitis, recently identified by the World Health Organization as a matter of global concern, now has its own mobile app. Antimicrobial Therapy, Inc., the publisher of The Sanford Guide, a reference for infectious disease treatment, recently announced the release of the Sanford Guide to Hepatitis Diagnosis and Treatment. The first mobile app of its kind for hepatitis treatment, it was unveiled at the51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Chicago. The app is designed to give physicians treating hepatitis patients real-time access to treatment options and other clinical decision support tools.

"A revolution is occurring in the treatment of Hepatitis C virus infections, similar in magnitude to the rapid change in HIV therapy in the mid-1990s," said Jeb Sanford, the guide's managing editor, in a press release. "A major difference between HIV therapy and Hepatitis C therapy is that patients can be cured of Hepatitis C infections. New drugs approved in 2011 are transforming therapeutic approaches to Hepatitis C treatment and many more new drugs are in development." The guide covers Hepatitis A treatment of acute infections; Hepatitis B treatment of chronic infections, management of exposure and prophylaxis in transplant patients; Hepatitis C diagnosis, epidemiology, natural history, clinical presentation, treatment settings and treatment; hepatitis immunization recommendations; and comprehensive drug information for anti-hepatitis agents, including use, dosage, dose adjustments, adverse effects, pharmacology and major interactions with other drugs.

Sexual transmission of HCV rare among long-term, monogamous couples: The HCV partners study

Terrault NA. Hepatology. 2013; http://onlinelibrary.wiley.com/doi/10.1002/hep.26164/full .

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Patients with chronic hepatitis C in long-term, monogamous relationships are at a very low risk for transferring the virus to their partner via sexual contact, according to a recent study.

Researchers interviewed 500 anti-HCV-positive patients with chronic HCV, along with their long-term heterosexual partners (minimum relationship duration of 36 months, median 15 years), about their sexual practices and lifetime exposure to risk factors for HCV infection. HCV RNA, anti-HCV and HCV genotype and serotype were assessed via blood samples, and phylogenetic analysis and sequencing also were performed.

Among the partners of patients with HCV, 20 tested positive for anti-HCV, including 13 who also tested positive for HCV RNA. HCV prevalence between partners occurred in 4% of cases, including nine couples with concordant genotype and serotype. Investigators calculated a minimum prevalence of 0.6% for infection attributable to sexual contact, assuming discordance among all partners who tested negative for HCV RNA, and a maximum of 1.2%, assuming concordance among those who tested negative for HCV RNA but were part of an antibody-concordant couple.

The estimated incidence of sexually transmitted HCV infection ranged from 3.6 to 7.2 per 10,000 person-years, with the estimated risk for transmission ranging from one in every 190,000 sexual encounters to one in every 380,000. No associations were observed between HCV positivity and any specific sexual activities.

“HCV transmission by sex from chronically infected persons to their heterosexual partners in a long-term monogamous relationship likely occurs, but is a rare event,” the researchers concluded. “Our results provide a basis for specific counseling messages that clinicians can use with their patients. These messages should be qualified given the limitations of the sample size, but they support the current national recommendations that couples not change their sexual practices if they are in a monogamous heterosexual relationship.”

Chronic HCV linked to hypertension, congestive heart failure

Younossi ZM. *Aliment Pharmacol Ther*. 2013;37:647-652.

- February 27, 2013

Patients with chronic hepatitis C are more likely to have hypertension, in addition to insulin resistance and diabetes, and also are at elevated risk for congestive heart failure, according to recent results.

Researchers evaluated data from 19,741 participants in the National Health and Nutrition Examination Survey between 1999 and 2010. The cohort included 173 patients with chronic HCV, with the remaining 19,568 classified as controls.

Participants with chronic HCV were significantly more likely than controls to be male (66.6% of cases vs. 46.1%; *P*=.0001), aged 45 to 55 years (41.9% vs. 20.4%; *P*=.0001) and African-American (23.5% vs. 10.5%; *P*<.0001). Those with HCV also were more likely to have hypertension (40.1% vs. 28.9%; *P*=.0201), greater insulin resistance (IR) (44.1% vs. 31.1%; *P*=.0301), and a history of tobacco use (76.2% vs. 29.9%; *P*<.0001).

When participants were divided according to age (younger than 65 years or 65 years and older), congestive heart failure was found to be more common among younger patients with HCV compared with controls (3.84% ± 1.50% vs. 0.89% ± 0.08%; *P*=.0467), but not among older patients. No associations were observed between HCV and cardiovascular disease when the cohort was stratified based on smoking status.

Advanced age, obesity and smoking were predictive of cardiovascular disease development, including congestive heart failure, ischemic heart disease and stroke (*P*<.05 for all). Multivariate analysis indicated independent associations between chronic HCV and IR (OR=2.06; 95% CI, 1.19-3.57), hypertension (OR=2.06; 95% CI, 1.30-3.24) and diabetes (DM) (OR=2.31; 95% CI, 1.18-4.54). Investigators also observed an association between chronic HCV and congestive heart failure (OR=2.49; 95% CI, 1.04-5.96), but not stroke or ischemic heart disease.

“Our study shows that [chronic HCV] is independently associated with three important metabolic conditions: IR, DM and hypertension,” the researchers wrote. “The association of HCV with hypertension is a novel finding. … All of these findings emphasize the importance of assessing the true impact of HCV, not only for its hepatic complications, but also for its extra-hepatic manifestations.”

A 'Killer' of a Reason to Treat Hepatitis C

Dr. David Johnson, Professor of Medicine and Chief of Gastroenterology at Eastern Virginia Medical School in Norfolk, Virginia.

Hepatitis C and treatment for hepatitis C have been an ongoing issue, and we have never been in a more exciting time for eradication of hepatitis C virus. Unfortunately, many patients with hepatitis C progress to develop cirrhosis. It is estimated that 25% of patients in the United States with hepatitis C have cirrhosis. An estimated backdrop is about 3.5 million patients. By 2040, it is estimated that this percentage will go up to 45% if left untreated. This is a real problem, not only because of the consequences in our medical care for these patients, but because of what we should do for them now. It has never been more exciting to treat these patients, but we are often held back by patients with cirrhosis or fibrosis, and we think that they may not tolerate the treatments as well or that they are too end-stage, that they don't really need to have these treatments.

An exciting article was just published this past month in *JAMA*.[1] It is a study that looked at patients with cirrhosis or bad fibrosis. All patients had hepatitis C and liver biopsies, which were classified by an Ishak score. The Ishak scores ranged from 4 to 6. What that means is that these patients had significant scarring of their liver and, in fact, most of the patients had cirrhosis; 27% of patients had an Ishak fibrosis score of 4, 19% had a score of 5, and 54% were very cirrhotic with a score of 6, which is the end of the fibrosis score.

All patients had hepatitis C and were entered into an evaluation. From 1990 to 2003, 530 patients were treated at 5 centers around Europe and Canada. They were followed for the endpoint of all-cause mortality. Secondary outcomes were liver-related mortality, liver-related failure, hepatocellular carcinoma, and need for transplant or decompensation. These endpoints were fairly significant. They looked at sustained virologic response (SVR), which was defined as the absence of a virus for 24 weeks after treatment. It would be a sustained treatment effect, and clearance of the virus would be expected to be maintained. The SVR at 24 weeks would be no virus.

The timeline for this study is 1990 to 2003, so many of these people were receiving monotherapy, pegylated interferon treatments, or consensus interferon treatments. A smaller percentage of patients received combination therapy with ribavirin. Only 34% of these people actually had an SVR. Of the patients who had an SVR, the all-cause mortality was 8.9% at 10 years. Of the non-SVR patients, the all-cause mortality was about 27%. The mean follow-up was 8.6 years, so the 10-year mortalities were calculated if they were available and there was a reasonable endpoint. If you put the numbers for mortality together and look at 8.9% vs. 27%, the number needed to treat to prevent 1 all-cause mortality is 6.

In my 36 years of being in medicine, I have never seen such a number needed to treat for an endpoint that is as strong as mortality. With pharma trials, we get excited when we have a number needed to treat that is 10-20, a medium range of good news for pharma trials. Here, we are talking about mortality. A number needed to treat of 6 is unheard of. If you look at hepatocellular carcinoma, the number needed to treat here was 5. The number needed to treat for decompensation and liver transplantation was 4. Cause of death, liver failure, was 4. We have never seen this type of number before for the endpoint of mortality.

(Cont'd) Interestingly, they also found a cofactor that was a subset risk, which was genotype 3. If you are genotype 3 and not treated, then you are 2 times more likely to have all of these consequences. We do know that genotype 3 tends to be a much more rapidly progressive disease, although genotypes 2 and 3 are easier to treat. If you don't treat them, they tend to more rapidly progress to fibrosis and cirrhosis. They also tend to be more associated with hepatic steatosis, an independent risk factor for hepatocellular carcinoma. For patients who are subset genotype 3, we need to be very germane in pushing this into a new paradigm shift of prevention of death and much less decompensation and all the consequences of cirrhosis. The endpoints here are so strong for all-comers and even more so for genotype 3, that we need to be treating these people.

Very interestingly, there is a parallel story related to coinfected patients. A paper was published earlier in 2012 regarding HIV and coinfection with hepatitis C.[2] The study had 19 patients who had fibrosis or advanced fibrosis. The numbers were not quite as implicit as the study we just talked about, in which all the patients had fibrosis or advanced cirrhosis. These patients had coinfection, and the number needed to treat was very much in parallel with what we talked about for hepatitis C infection alone. In fact, no HIV/HCV patients who had fibrosis on their biopsies had any related mortality once they had an SVR.

Where are we headed with this? I think we are headed to a discussion with patients with hepatitis C and fibrosis or cirrhosis. If you have ever been hesitant to treat these people, get over it. These patients need to be aware of an endpoint that is so strong with mortality, that they need to be treated. I am not talking about waiting for new therapies. They need to be treated now. With an endpoint of mortality and a number needed to treat that is 4-6 for mortality, liver mortality, and hepatocellular carcinoma -- if you can't convince them at that point, it's never going to happen. Don't sit back on these patients. We have never seen a number needed to treat with an endpoint of mortality that is this low. Oncologic interventionalists would be ecstatic if they could have a cancer regimen that would prevent cancer or treat cancer with this type of number needed to treat.

Get off the dime. Look hard at your cirrhotic and fibrotic patients. Don't wait for new therapies. In the era of triple therapy with boceprevir, telaprevir, and some of the new protease inhibitors on the short-term horizon, we have an absolute indication and an obligation to treat our hepatitis C patients with fibrosis and cirrhosis, in particular the hepatitis C patients who are genotype 3.

Look at this article. Think about it. Don't forget the HIV-coinfected patients as well. It gives you an interesting discussion next time you have one of these patients in the clinic. It is an exciting time for hepatitis C. Let's make a real difference. I look forward to our next dialogue in the prevention of cancer. It's your opportunity now to take this back to your patients and apply it. I'm Dr. David Johnson. Thanks for listening.

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Adult Viral Hepatitis Prevention Program Staff:

Robert Brawley, MD, MPH, FSHEA
Chief, Infectious Disease Branch
502-564-3261, ext. 4235
Robert.brawley@ky.gov

Kathy Sanders, RN, MSN
Adult Viral Hepatitis Prevention Program Manager
502-564-3261, ext. 4236
KathyJ.Sanders@ky.gov

"People use drugs, legal and illegal, because their lives are intolerably painful or dull. They hate their work and find no rest in their leisure. They are estranged from their families and their neighbors. It should tell us something that in healthy societies drug use is celebrative, convivial, and occasional, whereas among us it is lonely, shameful, and addictive. We need drugs, apparently, because we have lost each other.

Wendell Berry