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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

New Treatments to Reduce Liver Damage From Hepatitis B

You are listening to ReachMD, The Channel for Medical Professionals. Welcome to GI Insights where we cover the latest clinical issues, trends, and technologies in gastroenterological practice. GI Insights is brought to you by AGA Institute and Sponsored by Takeda Pharmaceuticals North America.

Your host for GI Insights is Professor of Medicine at University of Illinois, Chicago, Dr. Jay Goldstein.

Dr. Goldstein has served as an independent contractor, consultant and is a member on the speaker's bureau for Takeda Pharmaceuticals North America Inc. he has also been the recipient of funding for research grants and educational grants from Takeda Pharmaceuticals North America Inc.

Are there new treatments that can stop or reduce liver damage from hepatitis B. Here with an update of hepatitis B therapy is Dr. Scott Cotler, Associate Professor of Medicine and Chief of the Section of Hepatology at the University of Illinois at Chicago.

DR. JAY GOLDSTEIN:

Hello Dr. Cotler.

DR. SCOTT COTLER:

Hello Jay.

DR. JAY GOLDSTEIN:

Let's get right to the topic, what is hepatitis B and how prevalent is it?

DR. SCOTT COTLER:

Well hepatitis B is a virus that infects the liver and worldwide there are about 300 to 400 million people who are infected. In the US, the estimate is more like 2 million and many of these people are really immigrants from areas of the world where the disease is endemic.

DR. JAY GOLDSTEIN:

How is the disease transmitted?

DR. SCOTT COTLER:

Well, in areas where it's endemic, it is either vertically from mother to a baby at the time of birth or between young children at play who share blood. In the developed blood, it's horizontal or between usually young adults through sexual activity or sometimes through drug use or other means of parenteral exposure.

DR. JAY GOLDSTEIN:

What are the consequences of untreated hepatitis B?

DR. SCOTT COTLER:

Well, it can cause cirrhosis, complications of cirrhosis and liver failure, and liver cancer, and hepatitis B is really a major cause of liver cancer worldwide.

DR. JAY GOLDSTEIN:

Can we intervene? Can we treat these patients and avert those long-term outcomes?

DR. SCOTT COTLER:

Well, we know we can treat them. We now have really a number of drugs. Hepatitis B is an exciting because of all the new drug development. We can suppress viral replication. We can perhaps change the natural history in some cases and I think the big question is who should we be treating and long term can we reduce this risk of liver cancer?

DR. JAY GOLDSTEIN:

Can you give us any hints about whether we can or cannot, what is the problem with the data?

DR. SCOTT COTLER:

Well, there is one good study in patients with cirrhosis showing that treatment with lamivudine, which is one of the older oral agents can reduce the risk of complications of liver disease and can reduce the risk of developing liver cancer. What we need is more prospective data in patients who are not cirrhotic to prove that we can do this, but I will add that there is good data to suggest that virus level is associated with risk of progression of the disease either to cirrhosis or to liver cancer that comes from the R.E.V.E.A.L. Study. So the big question is if we can suppress virus level in people who are not cirrhotic, can we prevent these outcomes from occurring.

DR. JAY GOLDSTEIN:

We would like you to give us some principles about the goals of treatment for hepatitis B then.

DR. SCOTT COTLER:

Well, we have to break the patients up in terms of e-antigen positive and e-antigen negative patients and if you look at the e-antigen positive patients, there are really two groups, one is the people who are immune tolerant; if you acquire the disease at a young age, at birth or in childhood, people tend to go into a long-term immune tolerance state and in that state, we have high levels of viral replication, but normal ALT levels and no significant liver damage. Those people, at least currently, we don't tend to treat; however, overtime as people aged, the immune system kicks in and they go into an immune clearance phase where there is ongoing liver injury and over time there can be progression to cirrhosis, so we tend to treat these e-antigen positive patients who are in the immune clearance phase with the goal of achieving an e-antigen seroconversion. When that happens, they lose e-antigen, they become antibody positive and virus becomes undetectable and then we would treat for a consolidation period after that and then stop therapy and we want to help that patient to gain immune control so that the disease becomes quiescent. So that's the e-antigen positive group. For the e-antigen negative patient, again we can look at two different categories, one is the people who are in the low replicative state who have had an e-antigen seroconversion generally spontaneously and if they have quiescent disease, we tend to monitor them, we know their risk for liver cancer and sometime reactivation of their disease. Some of these people will develop viral mutations, either a precore or a core promoter mutation and then the virus starts to replicate again and they develop what's called antigen negative chronic hepatitis B and this the later phase of disease associated with more inflammation, more severe fibrosis, cirrhosis, etc. So, we want to target our therapy on the e-antigen negative patients on these people who have e-antigen negative disease and in that setting the goal of treatment is suppression of viral replication and, of course, when we suppress the virus, our other goal is to treat the liver disease and to reduce inflammation and either to inhibit fibrosis progression or even now we have some data that in some cases we can get regression of fibrosis if we achieve viral suppression.

DR. JAY GOLDSTEIN:

Do these principles hold true for cancer development?

DR. SCOTT COTLER:

Well, that's a very good question. I mentioned that we have studied earlier in the cirrhotic or early precirrhotic patients, we don't know for certain whether it holds true for noncirrhotic patients. We do know that in hepatitis B unlike other causes of chronic hepatitis that we see liver cancer develop in the absence of cirrhosis and so one of the hopes is and one of the things that needs to be proven is that if we can suppress viral replication that perhaps we can reduce this risk, not only of liver disease progression, but also the development of liver cancer.

If you are just tuning in, you are listening to GI Insights on ReachMD, The Channel for Medical Professionals. I am your host, Dr. Goldstein and joining me today to discuss update on hepatitis B therapies is Dr. Scott Cotler Associate Professor of Medicine and Chief of the Section of Hepatology at the University of Illinois at Chicago.

DR. JAY GOLDSTEIN:

Well, Scott, why don't you just give us an overview of the types of medications, how we classify them, and then we can go into a little bit more detail about each.

DR. SCOTT COTLER:

Now the first drug that was tried in true for hepatitis B was on modified interferon. After that we had the developments of the oral agents, the first being lamivudine, the next drug being adefovir, and after that came entecavir that was in about 2005 at which time pegylated interferon was approved for treatment of hepatitis B and then we had more recently telbivudine and finally tenofovir being approved for the treatment of hepatitis B. So what we have at this point is pegylated interferon and then we have nucleoside and nucleotide analogs oral agents that are very potent in terms of suppressing viral replications.

DR. JAY GOLDSTEIN:

Do we use these individually, sequentially, or in combination?

DR. SCOTT COTLER:

Right, good question. Well, there was a couple of big studies looking at combining lamivudine with peginterferon and while they improved viral suppression, it did not increase seroconversion rates, so combining an oral agent with peginterferon at least to date has not been shown to be particularly beneficial. Now, with regard to the oral agents if you look at the field of HIV or even hepatitis C, we want to sue more than one drug. The interesting thing in hepatitis B is that it looks for treatment naïve patients who don't have viral resistance. There really isn't any sound data to suggest that using more than one drug is more effective than using a single agent. In a couple of the drugs that we are talking about entecavir and tenofovir have very low resistance rates, so in general if you have a treatment naïve patient and they are going to use an oral agent, you can start with one potent agent that has a low rate of resistance. If you have a patient who develops resistance to a drug, we really do want to avoid serial monotherapy, so we tend to add a drug that doesn't have cross-resistance as opposed to substituting.

DR. JAY GOLDSTEIN:

How do you recognize resistance?

DR. SCOTT COTLER:

Well that's a difficult issue. We can do blood tests and you can send your sample off to a commercial laboratory and they can test for mutations that are associated with resistance, but clinically what you tend to see first is an increase in the viral level from the nadir and a virologic breakthrough is to find as a one log or 10-fold increase in virus levels from that nadir, and that should trip you off to one of two things; either the patient is not being adherent with their medicine which is a common cause for virus levels to go up or they have developed resistance.

DR. JAY GOLDSTEIN:

Having gone through this, we talked about the naïve patient and the low level of resistance in the community at first go and how patients do develop resistance, but truly what about the patient who has failed one therapy, do you go back into a different nucleoside agent or do you go to an interferon product?

DR. SCOTT COTLER:

Well, that would really have to be considered on a case by case basis. I mean there are some potential upsides to interferon and that there isn't an issue with resistance that at least with one year of treatment, the seroconversion rate in the e-antigen positive patients are a bit higher than with the oral agents. So if you look at the oral agents, you can catch up over the second year, but yes, in a patient who fits the profile and is motivated to take interferon, that would be one approach, or you could shift to another or add another oral antiviral drug, again that doesn't have cross resistance in order to achieve viral suppression. You have options because we have so many different agents now.

DR. JAY GOLDSTEIN:

Not only resistance is an important issue, but side effects of that medications, what are the side effects which one would look for in choosing a drug.

DR. SCOTT COTLER:

Well, pegylated interferon has the side effects that we know from hepatitis C and people can get flu like symptoms and cytopenia, fatigue, and depression, etc., although it doesn't seem to be as marked as we see in patients who has hepatitis C. With regards to the

oral agents, in general, they are very well tolerated. There are some specific things that I want to point out though, one is with regard to adefovir that there is a small rate of nephrotoxicity, about 3% over 5 years in people of compensated liver disease, but higher rates reported in people who have decompensated disease. So that's an issue for concern. Now, adefovir and tenofovir are very closely related agents, tenofovir is more potent, but seems to have a very uncommon association with nephrotoxicity, although there have been some reports of vancomi syndrome. A lot of the data comes from HIV patient who may have other reasons for renal insufficiency. Another agent that I mentioned just in passing telbivudine has an association with a myopathy and in the range of about 5% of patients will get a CPK elevation. So that is something to keep an aye on for. Beyond that these oral agents again tend to be very well tolerated and really have very limited side effects.

DR. JAY GOLDSTEIN:

Can you give our listenership a sense of the duration of therapy before going to consolidation?

DR. SCOTT COTLER:

Well if you look at the data with the oral agents in the e-antigen positive patients, again you are trying to achieve a seroconversion. About 50% will develop a seroconversion over 5 years, so you know, there is a cumulative rate of 20% at 1 and going up from there and generally people would treat for a year after seroconversion. So even in the e-antigen positive patients, we are looking at fairly long-term treatment. In the e-antigen patients, if you discontinue therapy, most will relapse. The vast majority will relapse. So at this point, we are talking about fairly open ended suppressive therapy in that e-antigen negative group.

DR. JAY GOLDSTEIN:

Got fascinating! What is it about hepatitis B that you would like to share with our audience that really sticks out in your mind?

DR. SCOTT COTLER:

I think one of the most important things is that we have to recognize the populations that are at risk and the new CDC guidelines suggest that all people who had come from an area of the world where the prevalence exceeds 2% should be tested. If you look at the global map, there are areas of the world where up to 10% or more of the population is infected, so if you are in your office and you see a patient from Asia, from sub-Saharan Africa, from South America, or someone who is an Alaskan Eskimo or from the Mediterranean areas, these people need to be tested. We need to recognize this disease and then of course we need to recognize, we need to test their family members any sexual contacts, etc. So the first thing to do is to identify the people who are infected and then to recognize that we have a whole host of new treatments that we do have good therapy with I think fairly limited side effects and we need to get these people evaluated and considered for antiviral treatment.

DR. JAY GOLDSTEIN:

I would like to thank my guest from the University of Illinois at Chicago, Dr. Scott Cotler. Dr. Cotler, thank you very much for being our guest this week on GI Insights. Thank you.

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