

## **Interview: Dr. Pockros on NM283 and Other Drugs Being Developed to Treat Hepatitis C**

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I recently talked with Dr. Pockros at the Digestive Disease Conference about the need for new medications to treat hepatitis C as well as about various drugs that are currently in clinical trials including NM 283, VX-950 and SCH 50304. Dr. Pockros has been at the forefront of HCV treatment and care since the beginning of the HCV epidemic and kindly shared his time and expertise for this interview.

### **Why are new therapies needed?**

The issues in order of importance are:

- *Efficacy* – we currently have efficacy for about one half of the patients so not everyone with hepatitis C can be cured.
- *Tolerability and convenience* is also another issue since the drugs are not particularly easy to take and require a lot of monitoring and lab tests.
- “*Special populations* “ – A third reason we need to develop new drugs is that some of the populations with hepatitis C, such as people with genotype 1, African Americans, HIV/HCV coinfecting, people with renal problems and others, *do not respond as well* to current therapies or some groups may not be able to take or tolerate current therapies.

The two current drugs to treat hepatitis C are pegylated interferon and ribavirin. Interferon is a biologic agent that helps to improve or boost the immune response and may have other properties that we don't fully understand. Ribavirin is a small molecule that by itself does not cure the virus, but when used with interferon prevents relapse during and after treatment.

### **Please briefly explain how some of these new drugs work?**

The small molecules that are currently under investigation are designed to specifically inhibit the viral enzyme that is the key to viral replication. The hepatitis C virus, when it enters a liver cell, must use viral specific enzymes in order to replicate, and we are trying to make drugs that inhibit the replication process by inhibiting those enzymes. These inhibitors should not interfere with human cells as they specifically target viral enzymes. This is the strategy we have used for HIV. The drugs under investigation will most likely have to be used with other HCV drugs including pegylated interferon and ribavirin, initially at least. Unlike the case with HIV, the goal for hepatitis C treatment is to eradicate the virus. There are some groups with hepatitis C for which the goal will be viral suppression, but we hope that most people with hepatitis C will be able to eradicate the hepatitis C virus with these new medications.

**What do you think of the ‘cure’ word?**

I use the ‘cure’ word with my patients. We have conducted studies going back to look at patients treated with both Schering’s Peg-Intron and Roche’s Pegasys in combination with ribavirin and we have found that about 99% of people who achieved an SVR are still virus free in the serum and in the liver. In cancer, after 5 years we use the term ‘cure’ and we should be able to use that word for viral eradication. At the end of the day if you call it a “durable sustained virological response” or “cure,” what’s the difference? Of course people need to be monitored and patients need to be informed that they can become re-infected.

**What are the small molecule drugs being developed?**

There are two classes of drugs that are currently being developed – protease inhibitors and polymerase inhibitors. There is also the helicase inhibitor, but to my knowledge no one has yet developed it.

There are many new direct antivirals being developed, including a polymerase inhibitor – NM 283 (Idenix), a protease inhibitor – VX-950 (Vertex), and a serine protease inhibitor – SCH 50304 (Schering).

**There are concerns about the potential for drug resistance with the new medications. What are your thoughts about the potential for drug resistance with NM 283?**

So far we have not seen any drug resistance develop in people who have been treated with NM283, but it doesn’t mean that it won’t occur eventually. Idenix is performing genetic sequencing to determine if drug resistance does develop with the use of NM 283. In fact, I think we have to expect some drug resistance to develop eventually in any drug that is a direct antiviral. This is one of the reasons why we will need two different types or classes of drugs given together. Also, the new combination therapies will most likely be given with or without pegylated interferon.

**Will we still need ribavirin?**

I believe that all direct anti-virals will initially need to be studied in combination with ribavirin included, as RBV has been key to preventing relapse in all trials thus far. Therefore, the next step would be to study ribavirin with NM 283. Also, since ribavirin and NM 283 are both nucleoside analogs, we have to study the drug interactions like we have had to do with HIV. But, I don’t think it will be a problem – but we need to conduct those studies.

I think the question that everyone is asking is can we leave ribavirin out. If we look at the NM 283 trial in non-responders the answer is no. If you push the dose of NM 283 high some people get the gastrointestinal side effects. However it happens that you can give it in a lower dose and it works in treatment naïve patients. So the strategy in treatment naïve patients may work out great, but in non-responders you will need to mediate the GI side effects of the higher doses of NM 283 or you are going to have to add ribavirin or both and that is what Idenix is working on. If you look at the non-responder trial, only 3% of patients discontinued treatment due to NM 283. One of the reasons that

they lowered the dosage is that 2 patients in the naïve treatment trial and 1 patient in the non-responder trials developed severe vomiting and dehydration, but these types of serious side effects were the exception rather than the rule. Most patients were able to tolerate NM 283. In the phase IIb trial of treatment naïve patients the use of anti-emetic medications is permitted to mediate the gastrointestinal side effects. The higher doses are not completely out of the picture and testing in animal models is continuing. Keep in mind that if you have ribavirin added you may not need those higher doses.

**Will we still need pegylated interferon?**

Yes, we are not at a point where we can replace pegylated interferon but eventually treatment will probably consist of direct antivirals to treat hepatitis C.

**Do you think that the addition of pegylated interferon will prevent drug resistance?**

Yes, I think pegylated interferon will have to be given with the new drugs but resistance may still occur with long enough therapy, likely with all of the direct anti-virals as is true in HIV.

**What are your thoughts about Albuferon?**

I'm not sure that a once every two week injection would make a whole lot of difference to patients. You may also run into adherence problems. But if it turns out that it would be effective in a once-a-month dose, then you could dose it in a doctor's office and that would be important because you could bring in a patient to the office for the injection and lab work. Another important issue would be quality of life. If Albuferon can show an improvement in quality of life then it would be an improvement over pegylated interferon.

**What about the new therapies for the populations who do not respond as well to current medications?**

Currently African Americans have a dismal response to current therapies, and we have to do better. Hopefully the addition of a direct antiviral will improve this. If you look at NM 283 in the treatment naïve study the antiviral response is quite brisk. Since the response of African Americans is affected by a lower immune response, the new antivirals should not be hampered by this, and that's the beauty of it. The question is, can you still get that antiviral response? Hopefully! In the NM 283 phase IIb study, African Americans are included so we should have some answers after the completion of the clinical trial.

**What about HIV/HCV Coinfection?**

You know the studies with the current standard of care, and I think the same steps will need to be taken with the new drugs. First you will need to test whether the new drugs interact with HAART therapy because that would inhibit what therapy the patient is on. Secondly, we will need to find out if HAART blocks the HCV antiviral therapies. It shouldn't, but we have to find out. Thirdly, we would have to study what combination of HIV and HCV drugs would increase the SVR rates.

**Have you heard about the small study where they used ritonavir, a current HIV medication, with other HCV drugs to boost the blood levels of HCV drugs?**

Yes, I think if you look at the current strategies with VX-950 dosing every 8 hours – this is like it was in the early days of HIV treatment. In the population with Hep C I think this would be quite difficult. I think if you had a drug that boosted the blood levels of the HCV protease inhibitor so that you only had to take it twice a day instead of 4 times a day – that would be a big improvement. Obviously, the most important factor for a new drug is efficacy, then tolerability followed by convenience. I think that after we develop new drugs with better efficacy and tolerability we will need to look at convenience. Of course, we will need to study ritonavir more and see if it causes additional side effects.

**What about SCH 50304?**

I think that it is showing benefit and could be effective. You have the added benefit of Peg-Intron and it should go forward with development. We will need many new drugs to treat hepatitis C. Look at the drugs to treat HIV – we now have over 20 drugs to treat HIV and we will also come to a point where we will have and need many drugs and combinations of drugs to treat hepatitis C.

**How do you see the various drug companies working together to create better therapies?**

I'm glad you asked that question. This October the FDA is having a hearing about developing guidelines for new HCV therapies. For instance, do we need to study combinations of different drugs together, and should we study various patient populations now rather than in the future? I think the FDA may issue guidelines from this meeting and this is a good opportunity for medical investigators, patient advocates and government officials to help shape these guidelines. When the FDA issues the guidelines it will determine the future direction of HCV drug development and clinical trials. I think this is where HCV patient advocacy could have a huge impact.

**In closing what would you like to say about NM 283?**

The drug shows antiviral properties, efficacy, in both treatment naïve and non-responder populations and appears to be generally well-tolerated in combination with pegylated interferon.

**In general, what are your thoughts about the new drugs under development?**

I've been involved with hepatitis C testing and drug development since 1989. This was before we had our first therapy to treat hepatitis C and I feel confident that we will continue to improve treatment. I feel that we will be able to cure 85-90% or more of patients with new therapies that are better tolerated and given for a shorter duration. Predictions about the future are very difficult, but I think it is accurate to say in 3 to 5 years that we will have new drugs to treat hepatitis C.

It's an exciting time to be involved with hepatitis C research. We have been waiting for these drugs for a long time. They have been very difficult to create and I am very happy and excited to actually have the new drugs in clinical trials because there is such an unmet need in the HCV population.

About Dr. Pockros:

*Dr. Paul J. Pockros is currently the Division Head of Gastroenterology/Hepatology at Scripps Clinic in La Jolla, California. He is also Co-Director of the Center for Liver Diseases at Scripps Clinic and a Skaggs Clinical Scholar at The Scripps Research Institute. In addition to his busy patient schedule, he has published over 150 articles/abstracts dealing with liver disease and is a national and international speaker on the subject of chronic viral hepatitis. He has published important observations in management of ascites, ITP (idiopathic thrombocytopenic purpura) in hepatitis C, decompensation of cirrhosis due to influenza, and results of various experimental treatments of chronic hepatitis. He is an invited reviewer for numerous peer-reviewed journals and has written numerous editorials, reviews and book chapters. With over 20 years of clinical research experience, he is also the Director of SC Liver Research Consortium, a clinical trial network made up of 47 sites and 100 Principal Investigators throughout the United States, specializing in liver research, which he founded in 1997.*