A future without interferon?

Interview with Jaen-Michel Pawlotsky

Jaen-Michel Pawlotsky

"I would say major scientific progress, modest humankind progress", said to me Jaen-Michel Pawlotsky, Department Head of Virology at the Hospital Henri Mondor, Cretteil, in France: this could be the synthesis of the gap between the social burden of hepatitis and the outcomes of medical advances in this field. It is a realistic statement and it underlines that sometimes science and research go faster that social consciousness and policies. This year World Health Organization celebrated the first Hepatitis World Day, and it was after a deep lobby activity started some years ago together by the international scientific societies -EASLD and AASLD- and the patient based organization World Hepatitis Alliance. Now there is a WHO resolution that recognize viral hepatitis as global threat, a public health concern. I had the opportunity to met prof. Pawlotsky during last Liver meeting in San Francisco, immediately after the speech he gave to the conference.

"Well, things have changed a lot scientifically. In terms of making priorities and improving screening and access to care things are going much slower and I think this is a kind of dissociation we are seeing in this field right now. The science is evolving very rapidly, we will probably discuss a number of advances that have been made, progresses are made in terms of new drugs coming, interferon-free regimen, etcetera, etcetera. Now, the global awareness of the problem, the knowledge that 130 million people are infected with HCV, active campaign for screening and ensuring access to care to these patients with the old drugs and eventually with the new drugs in future is something that I think is going very slowly and very late".

How we can describe the global burden of viral hepatitis?

Currently we estimate that 130 million people are infected with the hepatitis C virus worldwide, 350 million people are infected with the hepatitis B virus worldwide. Not everybody has access to therapy, for those who have access to therapy it's easy to control hepatitis B, you don't cure hepatitis B but you can control it with the drugs we have, entecavir, tenofovir. We see better and better treatments with hepatitis C and a lot of new data with very high cure rates but, again, I would like to insist on the fact that access to care, screening, active campaigns for screening and identifying patients and giving them the opportunity to have their disease controlled is going very slow and there are areas of the world where virtually nothing is done and I think that's a major issue that our community, the viral hepatitis hepatology community will have to tackle in the future.

Having a vaccine for the hepatitis B means that it is feasible the idea to eradicate hepatitis B virus from the world?

Yes, the vaccine is a very active one, it's very safe, it's something which works very well, the problem is that you have two steps. If you start vaccinating newborns, which is done in many areas of the world, you really decrease the burden of the disease and this is what is happening in China right now, they have been able

through their vaccination campaign to reduce the burden of HBV infections in young people tremendously, but you still have the old ones who are infected. So, your approach must be a double approach: you must obviously improve vaccination coverage all over the world, but you must also take care of the patients who have acquired the infection, are chronically infected and may need therapy. And this is a little bit of a challenge, vaccination is generally relatively cheap and very cost effective as a strategy, antiviral therapy is costly and this does not work everywhere and different countries have adopted different approaches for that.

For hepatitis C, we don't have any vaccine, but we are staring to have so many drugs..

I think what we have learned over the past few months, or weeks or even days here at this meeting, that it's very easy to cure infection, but we didn't have the right drugs to do that so far. Now these drugs are coming and we see that with good drugs. What is a good drug? It's a drug that is potent and has a high barrier to resistance, if you can sustain inhibition of viral replication for a few weeks, two months, you'll get to a cure. So, it's an easy-to-cure infection, the issue of vaccination is a different one. The point is that it's very difficult to develop a vaccine for this virus because of the immunology of this virus, the fact that it is highly variable, that infection does not protect against a new infection and there are other issues which is it has not become apparent to the vaccine industry that a vaccine for HCV was something important. I think it is still something important, I think in many areas of the world a vaccine would be useful, especially because for the same reason we discussed for hepatitis B, you have to treat the patients that have the disease but you also have to prevent new infections and protect the population, but right now this has not appeared as an obvious need and I would say that research and funding for vaccine research is very limited.

For HCV the standard of care is interferon plus ribavirin. Starting form this year we can add a protease inhibitor...

Yes, the new standard of care for genotype 1 is a triple combination of interferon, ribavirin and a protease inhibitor, either telaprevir or boceprevir. I think these two drugs are a progress but it's still interferon alpha-based and there are some issues and especially issues with tolerance of these combinations. But new new drugs are coming as well new combinations, as we learned at this meeting, previous meetings as well, but here in San Francisco the evidence is very compelling: we can treat and cure hepatitis C pretty easily without interferon. I think the next step will really be the interferon-free era and the question is which drugs, which duration, which patient and this is really we are entering maybe the final step of our quest for the "Holy Grail" of HEP C cure and this one will be which is the best overall interferon-free regimen for all patients infected with HCV. Then we have done that, the same problem we discussed earlier will remain: how do we ensure that access to care is possible for everybody? We have great treatments, they are very expensive, how can we treat everybody? So, it's the beginning of the end of the story, maybe.

In you speech you presented here in San Francisco a study Phase II that demonstrates the possibility to treat hepatitis C without interferon with a new compound. Can you describe the study?

It's a study which has been done in patients infected with genotype 2 and 3, they are relatively easy-to-cure patients and the study was based on the use of a cyclophilin inhibitor[1], it's a drug that targets host proteins involved in the HCV replication cycle. This drug was used either alone or in combination with ribavirin without interferon. The patients had the possibility of using interferon if they did not achieve an RVR, rapid virological response, undetectable HCV-RNA at week 4. I think the interesting result there is that with ribavirin and a reasonable dose of alisporivir without interferon, 50% of the patients were able to achieve a rapid virological response on treatment at week 6. We demonstrated that ribavirin added to this, if it's better to use alisporivir plus ribavirin than alisporivir alone, also demonstrated that some patients who did not have an undetectable HCV/RNA at week 4 got to an undetectable HCV/RNA at week 6 and now, this was interim analysis, we are waiting for the final results of the study and see if these patients will relapse or will achieve a sustained viral response. I am pretty optimistic they will achieve a sustained viral response without interferon, but this will be presented I hope at the next EASL meeting.

And what about the safety profile of this new compound?

The comparison of interferon-containing arms and non-interferon-containing arms gave an obvious advantage for the non-interferon-containing arms. The two major side effects have been associated with the use of alisporivir more frequent than in the non-alisporivir arms were, number one, nausea, which was a little bit more frequent, and, number two, hyperbilirubinemia, which is well-known effect of alisporivir. With the doses that were used in the trial, the elevation in bilirubin levels were pretty acceptable, very few patients did more than 3 times the upper limit of normal and no patient more than 5 times the upper limit of normal. So, on average, it was a modest increase of bilirubin that was dose-dependent and more important in the presence of ribavirin, no other major side effects to report.

So, we will meet in Barcelona to discuss the new results of the study..

I hope that in Barcelona we will be able to show you the sustained viral response results, but I am sure there will be many other studies show in Barcelona and we will probably have a lot to discuss them.

Andrea Tomasini

[1] DEB025 is the first in a new class of drugs called cyclophilin inhibitors. Unlike other compounds in development that target the virus directly, DEB025 is a host targeting antiviral that targets host proteins essentials for the replication of all types of HCV. The expected results is that this compound may offer an effective treatment option across HCV genotypes with a high barrier to resistance.