The future and the present of DAAs against HCV

Interview with Mark Thurz

"Do you want to say who I am for the microphone? So, my name is Mark Thursz and I am the Secretary General of the European Association for the Study of the Liver and we are here now at the 47th International Liver Congress in Barcelona and one of the most exciting things that we have seen this year presented at the meeting is a series of presentations on interferon-free regimes…".
It is not only the beginning of a press press conference, it seems to the beginning of a new era, the era of a different and possible therapy for people affected by chronic hepatitis C.
Prof Thursz, it seems that time is going to run faster than we expected…
Last year we saw for the first time a proof-of-concept study, a very small study from BMS presented by Anna Lok at this meeting showing that it was possible to cure a patient with chronic hepatitis C without the use of pegylated interferon and ribavirin. That was really exciting but none of us expected how quickly those results would be consolidated with other drugs and other regimens and different groups of patients, so it's been wonderful in many ways to see but it has made it really difficult for us to understand where the field is going to go over the next couple of years. What we'd really like to see is that an all-oral drug regimen goes into clinical practice within two years.

Why is so fascinating thinking about an interferon-free regime?

The problem with interferon is it has side effects,

similarly so does ribavirin have side effects, and in certain circumstances this limits the efficacy of the medication, so that side effects mean either dose reductions or termination of therapy. In some cases, patients can get very depresses, very tired, it also affects their ability to work or their family lives, it suppresses the bone marrow and that means in some cases they become susceptible to infection or susceptible to bleeding and so, and the ribavirin causes anemia, so it would be much better if can treat patients without these, without the drugs that cause all of these complications.

In a very short time we have a very complex pipeline, different classes and new direct antiviral agents. Before to describe these molecules, can you explain why it was possible in so short time to have a so huge pipeline for hepatitis C instead of other clinical conditions or infections?

Obviously that is an interesting question because we don't know why after many years of research, suddenly, so many of the pharmaceutical companies now have drugs that are so potent and so effective. I can't really give you an explanation for that, there has perhaps been a general move away from protease inhibitors. The protease inhibitors we know are good, we have two already available for use in Europa, telaprevir and boceprevir, but they are not particularly easy to use and they have to be used with the pegylated interferon. So, moving away from those, people have targeted the polymerase of the protein, the polymerase enzyme and particularly with nucleoside or nucleotide analogues these are affective across all genotypes, which again is a benefit, and resistance doesn't seem to be a major issue. The other target that people have been working on is the NS5A and I guess we as a community were slow to recognize the importance of this particular viral enzyme because nobody knew exactly what it does, we know it's involved in the replication of the virus but not exactly the specific function. What is clear now is that if you inhibit NS5A you end up with a very potent antiviral and what we have seen perhaps most effective is a combination of a nucleoside/nucleotide polymerase inhibitor along with a NS5A inhibitor and these seem to be very powerful.

Is going to change the landscape also of some established concept, for instance naïve patients having a protease inhibitors at the beginning and when we spoke about naïve patients we thought naïve to PI, a different way to define naïve patient.

Oh, yes, that is absolutely true. We will need one group of naïve to pegylated interferon and ribavirin and then we will be talking about a different group that are naïve in terms of their exposure to previous direct antivirals. Conceptually, one of the issues here is the emergence of resistance to direct antivirals which could present a problem in your selection of future direct-acting agents. One thing that is perhaps reassuring here is that we have learned that the viral variants that emerge and the suboptimal inhibition tend to disappear within 12 or 18 months, so probably developing resistance to one of these new agents is probably not long-lasting because the variants are not archived anywhere within the liver cells. The other important concept to understand is that with pegylated interferon previous treatment we defined a group of patients called non-responders, there are people where the virus really never was suppressed with pegylated interferon and ribavirin and we recognized those as being a very difficult-to-treat group.

Do you think that when we are going to establish clinical trials in order to evaluate direct antiviral agents without interferon background means that we have to evaluate vs. placebo?

I think the era of a placebo-controlled trial is well and truly over, so frankly is the era of pegylated interferon and ribavirin-controlled trial because I don't really consider that any longer to be standard of care in genotype-1-infected patients, perhaps it remains in place for genotypes 2, 3 and 4 but not for long.
What about the opportunity and the possibility to combine different direct antiviral agents? Here were presented many studies about this.

There are a couple of issues here obviously because some of the best-in-class are being developed by different companies. We can't quite control the situation that we get combinations of best-in-class all the time in the drug development era. Inevitably what will happen is, once these drugs are licensed and we know something about their safety profiles, as well as their efficacy profiles, then obviously the hepatological community of physicians will start experimenting with different regimes, which may be obviously that you may need different combinations depending on which group of patients you are looking at.

We have a lot of results and data regarding genotype 1 and what about the other genotypes of HCV?

I think for the first time we are beginning to see drugs coming through that have efficacy against genotypes 2, 3 and 4, as well as genotype 1. So, a lot of the new drugs are not genotype-restricted, the classes such as the nucleotide analogues, they are not restricted to just one genotype, similarly NS5A inhibitors, they work across the board.

There are also some concerns regarding the assay

that were used in clinical studies. I am referring to different sensibility of Abbot and Roche assays, could you comment about this?
Obviously, in these studies, the new drug development studies where we are really keen to know whether the virus has gone, then the sensitivity of the assay is absolutely critical, but we are now working at the limit of both assays capabilities and I think it will actually emerge over the next few months what is the best way of measuring, what are the key time points to measure, but at the moment I agree, there is some confusion that needs to be resolved.

Q:
Clinical trials enroll selected people. There are some populations within HCV that are in some way in a hurry because they have a different condition, a disease more progressed, they are transplant people or co-infected people, we haven't any data regarding the treatment with currently available protease inhibitors?

Well, at the meeting actually there have been two studies that have helped us along in this way. One in co-infected patients showing that it is feasible to use protease inhibitors in patients with HIV. Obviously, drug-drug interactions need to be carefully managed, but what the study tells us is that is entirely feasible and that when protease inhibitors are used in combination with Peg/Riba in this patient group it can be very effective, it certainly improves the sustained virological response rates or it's expected to. Similarly, it is possible to manage drug-drug interactions in patients who are on CNI drugs, tacrolimus or cyclosporine, post-transplantation. We are going beyond that, there are other groups that the new regimes may benefit, so we have not really been able to treat patients who have end-stage liver disease decompensated cirrhosis because they can't tolerate pegylated interferon and ribavirin. We now know that here are regimens available that will allow those patients to access drugs and I know that protocols are currently in development for those patients.

Cost about new drugs is a central issue, but here there was presented also a study related to the disease burden. Can you comment how to manage the amount of money we have to spend now for a possible cure vs. the disease burden of hepatitis C in Europe?

It's true, of course the burden of viral hepatitis in Europe is high and potentially the cost of treating

patients is one of the reasons why Health Agencies and Governments have perhaps not been taking the epidemic so seriously, but we all know that if you fail to take action now the cost in the future will be much higher, so in the long term if you take a longer time horizon, it's more effective to get on and treat patients at the point in which they got chronic hepatitis because studies from Italy show that by the time you get to cirrhosis, transplantation and hepatocellular carcinoma, there is an exponential rise in the cost of managing these patients. We don't know what the cost of the new drug regimes are going to be but there is no doubt at all that the cost of treating a patient with chronic hepatitis is definitely going to outweigh the concept of delaying until the patient has symptomatic disease.

It's difficult to define what means in hepatitis C early treatment?

The early treatment has perhaps two concepts. There is those patients who have recently been exposed to hepatitis C or present with symptomatic hepatitis C infection, so you could say those are acute infections, early treatment seems to be pretty effective in that group and they actually respond extremely well in the early phases. The other concept transposes early in the stage of disease in patients who have chronic infection, so that would be the phase before they get to fibrosis scores of 3 or 4 on a Metavir scale.

Thanks to direct antiviral agents we are going to define the 12 week sustained viral response, now we are speaking also about 4 week as we are, that means that we have a tool in order to reduce the costs?

So, being able to monitor the point at which you know confidently that a patient has been cured, this is clearly important, so for the last few years we have used SVR24, 24 weeks after the end of treatment we measure whether a patient has the virus or not. We are now confident that SVR12 is just as informative as SVR24. SVR4 probably overestimates the success of a treatment regime in many cases, but SVR4 gives a very good indication of what the outcome is going to be for the trial. So I am not sure that licensing agencies necessarily are going to take SVR4 on board, but I have no doubt that SVR4 data is not going to really be regarded as interim but is going to be very indicative of SVR12 result.

Speaking about real life. Imagine a patient arriving in your clinic now. You know that he/she could be treated with the new drugs now available, but these drugs could have some noisy side effects. You know that a lot of new drugs are coming probably in few years with a better safety profile. What do you suggest to your patient?

This is a really good point actually because if you have advanced disease, so you have got cirrhosis already as a patient, then there is no doubt we need to get on and treat you, but for pretty much every other patient, well, if it was me, I would choose to wait at the moment because in two or three years' time there is a treatment option that is easier to take, it's shorter duration, probably far less side effects and more effective and it's going to be quite difficult to recommend anything other than waiting for most patients.

So many DAAs will pone –shortly- the problem of the comparison between them, in order to decide which one should be used first. EASL is the most authoritative scientific society, now how can you approach the story? This is a very crowded world…

A:
So, this is an issue I alluded to earlier on that probably the combinations of direct antivirals that get licensed may not necessarily be the optimal combinations for patients. So, we have seen what happened in HIV that, after combinations were licensed, then the community set about resolving some of these issues with clinical trials. EASL of course doesn't have the funds to run these trials by itself, I think EASL's role here is to make sure that people are extremely well educated and for us also to lobby at the European agencies, the DG Research, as well as Member State funding bodies, for trials to be funded so we can get to the bottom of this.

Last question. In the future may be that, having so many choices, tailoring therapy will be the right way to address hepatitis C?

There is no doubt about it that a patient with end-stage genotype 4 is unlikely to need the same treatment as a naïve patient with early disease and genotype 1. So, yes, tailoring will be critical, we are not quite sure at this point in time how important on-treatment virological monitoring is going to be, but that may also be part of the complexity of managing these patients in the future.

Not every physician can address this kind of issues…

Well, it's interesting, we could conceive now of simple straightforward regimens that might be applied in primary care settings rather than in big hospitals' specialist units in the future. The specialist units will then be left dealing with the more complicated patients with resistance issues, advanced disease and that sort of thing. ■

Andrea Tomasini