DAAs: the lexicon of a changing paradigm

Interview with Heiner Wedemeyer

"When we will have the new HCV drugs which are in development, when they will came to market, it will be on us –clinicians, scientists together with the patients- to further optimize also these new tools- tell to me with emphasis Heiner Wedemeyer, managing senior physician and assistant professor in the Department of Gastroenterology, Hepatology and Endocrinology at Hannover Medical School. We are living the beginning of a revolution –the new story of HCV therapy thanks to DAAs, but I would like to start this conversation speaking about the possible "end" of the story: the future of hepatitis C treatment…

"I think the future of hepatitis C treatment will be the same as we have today, and this is individualized treatment for each patient. Right now, we are using protease inhibitors in combination with ribavirin. For the first time the labels of these new compounds include already the concept of response-guided therapy, which does mean that in some patients you may have a shorter treatment duration, in others you need a longer treatment duration. Obviously the benefit is to enhance response rates in each individual patient, also to save costs, to reduce the burden of treatment, to reduce side effects and thereby to optimize treatment in each patient. This concept is now part of the label, but I see that the future of hepatitis C treatment will even further expand this concept of personalized medicine: individualized treatment for each individual subject. Obviously, we would like to have a treatment one-size-fits-all, let's say for three months one pill a day and we cure all patients. But what we have learned over the last six months and what we have listened during this EASL meeting in Barcelona, is that most likely for some patients this may work but I think that hepatitis C is a disease where we will need to optimize treatment for each individual patient, and this should be possible. The future of HCV treatment can be quite interesting: some patients may be cured with a very short treatment duration, other patients may need a longer treatment duration, and this is based on the compounds we are using, and also this is based on in-

dividual patient profiles, including certain their characteristics like, genetics, age and, very importantly for us being hepatologists, liver disease. The stage of liver disease matters. We already know this for interferon-based treatment: patients with more advanced liver disease, liver cirrhosis, fibrosis, they show rather poor response to the current treatment. This also holds true in the context of triple therapy, where interferon/ribavirin is given in combination with the protease inhibitors, so the protease inhibitors are not able to overcome interferon non-responsiveness which is more a problem in patients with advanced liver disease. So, the future will need to show whether the same also holds true when we have more drugs available, but this is on us to investigate.

We are living is a changing paradigm. We should describe this try to figure out how "old words" have now different meanings. For instance, we could start from "naïve" patient…

Well, old words have different meanings indeed, the paradigm will change. We have, let's say, patients that have been treated with interferon or untreated patients: the response to treatment needs different terminology, the patient characteristics need to be studied in a different context whether the old classical characteristics - old patients, young patients, men, women, different racial backgrounds they also have the same meaning in the context of the new treatments. I think most likely certain characteristics will also be important in the future, while others will be of less importance. The same holds true for patients that may have been exposed already to interferon and ribavirin or the new protease inhibitors, and there an additional player may become important and that is the type of response to this previous treatment. So, by treating patients we are changing the patients. First of all, you are changing the virus. A protease inhibitor, if treatment failed, causes resistance: when does this wild-type virus come back? Does this resistant virus somehow is maintained at a higher level and therefore impacts future treatment? In addition, when we are exposing patients to interferon/ribavirin, this may also have consequences for subsequent treatment: again, the virus is changing but also the host is changing when you expose them to such, let's say, strong treatments for rather long time. The detailed importance of these respective factors, again, have to be studied in the context of the different regimens to be tested in future.

Do you think we need -and is another word- a different "nomenclature" of the drugs?

We have different classes of drugs. We have direct-acting antivirals, which mean that really the virus is targeted specifically by the mode of action of the respective drugs, and then we have drugs which target, for example, host enzymes; then we have drugs that are somehow altering the immune system and are aiming to enhance immunity against HCV. Terminology is important for drugs, but terminology will be also important for assessing treatment response. Currently, we are using in hepatitis C terms like "Rapid Virological Response": "rapid" is defined by week 4 response, which is quite frankly ridiculous, because a rapid response in these days, in 2012, I consider response much earlier than after 4 weeks, or Early Virological Response, at week 12, which is currently the end of treatment in most treatment regimens. So, we have proposed a new nomenclature determining treatment response which is more descriptive based on treatment week and the level of virological reduction. This new terminology should also allow us to compare different trials, to compare different treatment regimens and really to judge whether in the end one treatment is better than the other.

Another word that is critical is "assay".

We are right now determining in-treatment response by reduction of viral load in these patients and then we have the endpoints or the interim points of suppressing viral replication. Biologically, we have to keep in mind that all these assays that try to detect viral loads have slightly different performances: this may have major impacts in the context of treatment response or response-guided therapy. For example, if a patient is negative after 4 weeks of treatment, then you can shorten treatment duration according to the current label, but negative may be different between different assays. I think all the clinical investigators, as well as the companies which are providing us with different assays, have really come to a consensus that we do not overtreat some patients. I don't want to expose patients unnecessarily to another 24 weeks of interferon treatmen,t which really impairs quality of life, simply based on differences in performance of assays. On the other hand, I don't want to risk that a patient who has gone through a hard therapy is experiencing a relapse, because I am treating him too short because my assay was not applied in an appropriate way at certain time points during treatment. This is what we also learned during this EASL meeting: that indeed assays matter and that performance matters, but also we as doctors have to learn to read the assays in the right way: it is not only that assays differ, it is on us to understand the assays.

Another word that is different is now "clinical trials" because we should now to design them in a different way.

Clinical trials are always a challenge to be designed in the best way for the patients, but also the companies have to fulfill requirements that are set by the Agencies. FDA and EMA have to follow rules, they have their own standards internally, obviously aiming to that only safe drugs are at the end approved and licensed. This agencies have their standards and for hepatitis C. Again, we are right now observing a paradigm shift which is quite fascinat-

ing. One paradigm shift was over the last two-three years, that we can now test two investigational products at the same time. It was unbelievable three, four, five years ago, we could only test one compound in addition to whatever standard-of-care and now in hepatitis C. Now we are testing two compounds at the same time and I have seen protocol proposals even testing three investigational compounds which have not been licensed at the same time: this is a change in paradigm. The future will need to show whether also we see changes in trial design, in terms of our comparators. Because we have a problem in hepatitis C: sometimes you start a program and you tested against an old comparator which at that time was the standard of care, then in between you have a new standard of care which gets approved and then already the next generation of treatment regimens is in clinical development. So it's for us quite hard to design the trials and then to go through this, when at the time of finishing your trials your comparator is no longer the current standard of care. We have to think about concepts how to overcome this problem, and obviously finally ,the patients wish that we have fast trials. I don't want to go for a trial that takes two, three years before everything is analyzed, finalized, etcetera, because obviously this would delay drug developments. I am seeing patients dying from hepatitis C every week and these patients don't want to wait for long-term trials.There there is a lot of discussion how we can basically speed up drug development without taking too many risks, because also for all the HCV drugs, with all the excitement of the new response rates, of the possibility to cure patients without using interferon, we still have to keep in mind that you have to follow the standard rules. I don't want to expose my patients to unexpected side effects, I don't want to expose my patients to unnecessary risks: therefore we have to balance risks but also needs of these patients, which always is something which needs to be discussed, and there is ongoing discussion.

Another word that you anticipated now has now different meaning is "time".

Time is always an issue. During the old days, we have been treating patients for 48 weeks, sometimes for 72 week. Now we have learned that you may cure HCV in 12 weeks, maybe in 8 weeks, in some patients we have the suggestion that you may even cure chronic hepatitis C infection in 4 weeks, which is I think quite fascinating. So, the treatment duration will differ between different patients. An other aspect related to time is the time waiting for until the new drugs will become available: does a patient have time to wait or is there not enough time to wait for?. Treating liver diseases, we are quite fortunate: not in every patient, but for many patients we have time, and we should not overtreat patients too early, to expose them to side effects of interferon.In some patients it does not really matter if you start treatment next week, in one year or in two years. On the other hand, there are patients for whom time matters. I don't want to not treat a patient and then see that this patient will develop hepatocellular carcinoma in one year. Again, it's time of personalized medicine. It's individualized treatment: you have to identify the best time point for each patient to initiate treatment, based on the drugs that are available at that specific time point.

Another word with different meaning is "strategy".

Also treatment strategies will differ in future. We will have completely different strategies, different concepts to treat hepatitis C virus infection. One concept, one strategy is simply to block HCV replication and thereby to cure HCV. A completely different strategy is to use treatment that is based also on enhancing immune responses against the virus. We may even combine these different strategies in the future to further optimize treatment and, finally -I am coming back to this again- I think the strategy of the future will be to individualize treatment of hepatitis C virus infection based on individual patient characteristics, based on specific properties of the respective treatment regimen to be studied.

You open the door to another word of our new lexicon: "safety"….

Safety comes first in drug development. I mentioned this already: we should not expose our patients to unnecessary side effects of the current treatment, and the current treatment has safety issues. As we have learned in the recent months when patients with more advanced liver disease have been treated with a triple therapy of protease inhibitors plus interferon plus ribavirin, if you treat patients with more advanced disease, the likelihood that these patients can experience a severe infection, that they may die from this treatment is obviously higher. We have to select these treatments very carefully, not exposing our patients to unexpected side effects, unexpected safety issues using investigational compounds. Fortunately, so far the safety profile of the new compounds seems to be very good: I think we can give hope to our patients that indeed future treatment will be much easier and will cause less side effects. However, for most of the compounds we are still in Phase II or early Phase III and there are always surprises and some are bad also, this in drug development has been always the case, so before really giving too much hope, before, let's say, putting the patient into positions where they don't want to have anything else before the new drugs come, you always have to keep in mind some drugs may not make it to the market: safety comes first.

We are sailing in a crowded sea of choice, how to make "comparison"? That is another word that has now a different meaning.
As I mentioned before, we need to compare treatment responses between different drugs on very clear defini-

tions. The assays have different performances and the cut-off of responses needs to be defined. Is it that the virus is completely gone by the assays we are using, is it a certain threshold that we measure at certain time points? This is something which is important during treatment, to compare potency of drugs. However, in the long term it's easy for us, because we have a very good endpoint and this is cure, the virus is gone, and cure is the same goal for every treatment we will explore: every treatment strategy has only one goal which is cure. How to define cure? Currently, we are measuring HCV RNA 24 weeks after treatment has stopped. During the last year the FDA has approved another endpoint, SVR12, so cure after three months after the end of treatment is acceptable, which is fine. But I think we need to study also for the upcoming new interferon-free treatment regimens whether this holds true for every patient, or whether some patients may not experience a late relapse after 24 or 36 weeks. So, we have to do our homework, we have simply to follow these patients but, once this is achieved, I think all treatment regimens are comparable and the virus needs to be eliminated from the body.

Another hard word is "cost".

Cost is an issue, my personal opinion is that we all working in the medical health systems have a responsibility to use the resources in the best way. Resources will be limited, there is no way that we can extend treatment cost for whatever and we all have to see that really: we have to pay every price in the end, if is any increase in cost to be justified also in the context of other health burdens. I have never seen that a new treatment reduced costs, which is unfortunate, but obviously this is something we have to investigate. Just for example, right now we have two options: we have telaprevir or boceprevir in combination with interferon/ribavirin and these drugs have different costs and different treatment groups. I think it's our responsibility to consider this in treatment decisions. What the prices will be for the future treatments, we have to see and I think this is a discussion we should start again when these drugs are on the market.

We can say that from the EASL in Barcelona we are going to open the door to the real life for people with hepatitis C.

Well, real life treatments, you mean real using these drugs in real life right now. We can see that we should be very careful in just playing around with the drugs. Here we have to really follow the guidelines. My strong recommendation to all of my colleagues is that we don't play too much around and if you want to use these new drugs in a safe way, also to use not to waste resources, you really have to follow guidelines. It's our responsibility as being experts in the field, as being involved in society, to define the rules how these drugs can be safely used in patients with chronic hepatitis C.

When a patient arrives in your clinic, now knowing that there is a lot of future opportunities, how to make the right choice now looking to the next options?

Tthis is obviously a very important question and, as I mentioned earlier, we are now entering the phase of really individualizing treatment, of personalized medicine. You have to discuss each individual situation with each patient. So, what is the medical need for treatment of this patient? Does this patient need to be treated now to prevent side effects, to prevent decompensation of liver disease? On the other hand, we also have to consider what are the other circumstances for these patients. So, can they afford being exposed to interferon for 24-48 weeks? May this have consequence for their profession? Can they still continue work? And, on the other hand, what is the patient wish? How much is the patient suffering from this infection and not necessarily from liver disease? And we are discussing this with each individual patient also considering and keeping in mind that new treatments will be available in three, two, three, four years, which hopefully will have less side effects and which will lead to cure…. We discuss this on an individual basis with each individual patient. This takes time, but this is also fan and this is a great opportunity to really have the best treatment for each individual patient and I think this is our responsibility as being doctors in this field. ■

Andrea Tomasini