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EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

The International Liver Congress 9-13th April, London

by Professor Markus Peck-Radosavljevic
Secretary General of the European Association for the Study of the Liver. (EASL)

The International Liver Congress (ILC) 2014, EASL's flagship meeting, is approaching fast and will open on April 9th. The Governing Board of EASL was very successful in putting together a high profile scientific and educational program, which will attract a lot of international attention from within our own community as well as the press and media worldwide.

The highlight of the educational program this year will be the EASL Postgraduate Course, which will focus on the treatment of viral hepatitis. In addition to the Postgraduate Course, the program will be supplemented with Joint Workshops between EASL and a number of international medical associations in the field of liver disease, covering a wide selection of important educational topics in the early morning workshops, with clinical symposia, as well as the grand rounds.

The scientific program is set to be even more exciting this year, as indicated by a record-breaking 2, 826 abstracts submitted to the ILC. Amongst these, the most anticipated ones will be those presenting the data of a large number of phase-3 trials of all-oral drug treatments for chronic hepatitis C. But while these trials will make most of the headlines, the ILC offers much more than just the treatment of viral hepatitis.

Non-invasive evaluation of liver disease, portal hypertension and also treatment of primary biliary cirrhosis will represent other highlights of the ILC, just to mention a few. From a public policy point of view, the hot topic will be the launch of the WHO guidelines on the treatment of chronic hepatitis C during the ILC in London. Recently, WHO has compiled guidelines on the management of hepatitis C, which go beyond what is standard treatment in Western Europe or the US and it will be interesting to see how they envisage treatment of chronic hepatitis C in resource-limited settings. The WHO guidelines will be discussed during the public health session as well as during a separate symposium dedicated to the WHO hepatitis C guidelines.

I am sure that the program devised by the EASL governing board will be able to satisfy the needs of professional hepatologists as well as provide a stimulating learning atmosphere that will make the attendance at the ILC a very remarkable event.

So, I cordially invite you to join us in London in April at the 49th EASL congress and I hope that many ingredients will contribute to what we think will be our largest International Liver Congress to date.

Professor Markus Peck-Radosavljevic
Secretary General, EASL
Stellvertretender Abteilungsleiter
Universitätsklinik für Innere Medizin III
Klinische Abteilung fur Gastroenterologie und Hepatologie
Währinger Gürtel 18-20,
A-1090 Wien

Email: markus.peck@meduniwien.ac.at

Further information regarding ILC 2014 can be found at the EASL website: www.easl.eu

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Deferral of treatment in HCV patients: Risks and benefits

by Professor Alfredo Alberti
University of Padova, Italy

Until 2011, the only therapy for chronic hepatitis C was dual combination of Peg-interferon and ribavirin, used for more than ten years with excellent results in patients with well-compensated liver disease and infected by the "easy to treat" HCV 2 genotype and, although with somehow less successful outcomes, in those with HCV-3. The results of dual therapy were far from optimal in HCV-1 and HCV-4 genotype patients and in those with advanced liver disease, here largely independently of the HCV type.

In 2011 a new treatment strategy became available for HCV-1 infected patients, the so called "triple therapy" with a direct antiviral agent (DAA) (boceprevir or telaprevir – both being first-generation HCV protease inhibitors) added to Peg-IFN and ribavirin. Triple therapy arrived with an excellent pedigree from registration trials, which reported statistically significant improvement in rates of definitive cure with HCV eradication (SVR) in all HCV-1 infected patient subgroups, including those who had previously failed dual therapy [1-4].

For this reason, triple therapy was strongly recommended by national and international guidelines as the new standard of care for HCV-1 infected patients and was expected to be rapidly and consistently implemented in clinical practice, particularly in the large cohort of patients who had been warehoused in recent years, waiting for these new therapies. However, the clinical impact of triple therapy appears to be not as great as expected. Although most guidelines recommended triple therapy for all HCV-1 patients with progressive disease, the number of those treated is far below the numbers of cases with such an indication. There are certainly several reasons for this discrepancy: although the overall efficacy of triple therapy is distinctly superior to dual therapy, both DAAs work best in early to moderate disease and their efficacy is reduced in patients with more advanced fibrosis. Furthermore, side effects are certainly more frequent and severe, monitoring is demanding, and there are also the issues of several drug-drug interactions and of pill burden and adherence. Last but not least, the most severe complications have been reported in patients with a more advanced stage of compensated cirrhosis, particularly those with portal hypertension [5]. Thus, exactly those patients who were warehoused waiting for triple therapy, are those now considered by most treaters to have a doubtful risk/benefit ratio with such treatment. On the other hand, patients with a mild form of liver disease, are still waiting for easier to take and to tolerate regimens and look forward to receiving IFN-free therapy

Indeed, the main reason that is currently reducing the number of patients started on antiviral therapy for HCV in most clinical units is deferral, either proposed by the clinician, or requested by the patient, and motivated by the perplexity of proposing or of receiving IFN-based therapy, in light of current great expectations for the imminent availability of IFN-free regimens of great efficacy in eradicating HCV in most treated patients with short treatment duration and minimal side effects.

Indeed, already today in the US, and very soon in Europe, patients infected by HCV-genotypes 2 and 3 have or will have the possibility to be cured orally with sofosbuvir and ribavirin, given for 12 to 24 weeks.

Patients infected with HCV-1 will have to wait a little bit longer, but all experts agree in forecasting the availability of oral regimens for not later than 2015, based on the combination of 2 or 3 DAAs, which will cure >90% of HCV-1 infected patients with minimal side effects.

Therefore, there is much grounds today for considering deferral of therapy as a logical option for many patients with HCV. However, deferral should be decided on a case by case basis taking into consideration the pros and cons of such a strategy.

Clinicians should discuss immediate treatment or deferral with the patient in light of current and future therapeutic options, without using pharmacological progress as an alibi to warehouse reluctant patients. Rather, as Aronsohn and Jensen recently argued, clinicians "have a moral obligation to ensure that patients understand risks and benefits of deferral, just as they would if treatment was given"[6]. This "informed deferral" should encompass all the pieces of the puzzle including: a discussion of the difficulties of accurately staging hepatic damage; uncertainties regarding the prediction of fibrosis progression; and the vagrancies of clinical development and regulatory approval, which means that the launch and implementation of new drugs are not fully predictable.

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However, it is necessary to balance these drawbacks against the potential benefits of newer treatments to avoid forcing unnecessary acceptance of current therapy. The benefits of deferral are clearly related to the possibility of being cured in the near future with IFN-free regimens, that appear to ensure a very high rate of SVR to most (>90%) patients with excellent tolerability, thus avoiding the frequent and often severe side effects of IFN-based regimens, with the unpredictability of achieving SVR. Obviously, there are some risks involved with deferral, as the disease may progress to a "point of no return" while waiting for IFN-free regimens, which may be delayed in their availability for registration, or regulatory, or reimbursement issues.

Against this background, physicians should consider deferral, firstly, for patients with advanced disease for which there is no therapy and, secondly, for those with mild to moderate disease, characterized by low fibrosis, modest disease activity and a favorable previous course. Several tools now allow clinicians to monitor chronic HCV and reintroduce treatment should the disease progress. Warehousing is also rational for patients with contraindications to IFN or who have already failed triple therapy. Overall, clinicians need to be extremely cautious when proposing (or accepting the patient's request for) deferral in people with a progressive form of compensated liver disease. Accordingly, expert hepatologists are needed to carefully monitor and manage patients with chronic hepatitis C and not delay therapy if there is compelling evidence of progression.

In conclusion, against the backdrop of the moderate efficacy of dual therapy and the limited clinical success of first generation DAAs, the realistic prospect of new antivirals intensifies the argument for warehousing selected patients. Deferral is now a logical option for those with mild to moderate disease, in parallel with monitoring of disease progression, as well as for people with advanced disease who do not have any other treatment options. Nevertheless, deferral needs to be an informed decision, ensuring patients are made well aware of the risks, benefits and complexities of deferring treatment.

References

1. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M; REALIZE Study Team. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011 Jun 23;364(25):2417-28.

2. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S; ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011 Jun 23;364(25):2405-16.

3. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R; HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1207-17.

4. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar31;364(13):1195-206.

5. Hézode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, Poynard T, Samuel D, Bourlière M, Zarski JP, Raabe JJ, Alric L, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Métivier S, Tran A, Serfaty L, Abergel A, Causse X, Di Martino V, Guyader D, Lucidarme D, Grando-Lemaire V, Hillon P, Feray C, Dao T, Cacoub P, Rosa I, Attali P, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP; CUPIC Study Group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol. 2013, Sep;59(3):434-41.

6. Aronsohn A, Jensen D. Distributive justice and the arrival of direct-acting antivirals: who should be first in line? Hepatology 2011;53:1789-91.

Professor Alberto Alberti
Professor of Gastroenterology
Department of Molecular Medicine
University of Padova
Padova
Italy
Email: alfredo.alberti@unipd.it

AASLD 2013:
New drugs for chronic hepatitis B

by Dr. Willem P. Brouwer, and Professor Harry L.A. Janssen
University of Toronto, Cananda and Erasmus University Rotterdam, the Netherlands.

Current first-line treatment regimens for chronic hepatitis B (CHB) are unsatisfactory in terms of durability of response off-treatment. Nucleos(t)ide analogues induce a profound suppression of hepatitis B virus (HBV) DNA in more than 90% of patients during continuous treatment, however they do not induce a sustained off-treatment immune response. In contrast, finite peginterferon (PEG-IFN) treatment leads to more sustained off-treatment response, yet this is only achieved in approximately one-third of CHB patients. Therefore, more efficacious immune modulating drugs are required. Here we provide an update on the new drugs for CHB as presented at the AASLD meeting in Washington 7-11th November 2013.

Animal studies: Therapeutic vaccination.

A new viral-vector based immunotherapeutic (TG1050), which is based on a non-replicative adenovirus serotype 5 vector encoding for a fusion protein composed of a truncated Core, a modified polymerase and HBsAg domains, showed the capacity to induce high levels of T-cells targeting hepatitis B virus (HBV) Core, Polymerase and HBsAg domains after a single injection in an HBV mouse model. The induced T-cell response showed itself to be multispecific, polyfunctional and long-lasting, while a transient control of HBV viremia was observed. This therapeutic vaccine will enter good manufacturing practice and phase 0 testing in 2014.

Phase I study: Immune stimulation.

The oral Toll-like receptor-7 (TLR-7) agonist GS-9620, which is a stimulator of the innate immunity, is hypothesized to induce a more profound innate immune response to control HBV. It leads to sustained viral load and HBsAg reductions in animal models, and showed to up-regulate interferon-stimulated genes (ISG) and CCL8, without systemic IFN-related adverse events in healthy volunteers. In the current dose-escalation study, patients received GS-9620 doses of 0.3, 1, 2, 4 mg or placebo. GS-9620 was well tolerated and did not induce grade 2-4 hematological abnormalities. Moreover, it was shown that for these genes the mRNA expression was up-regulated for all GS-9620 doses, whereas no increase in serum IFN-α was noted. However, with regard to efficacy, disappointing results were observed. The up-regulation of the ISG-15 and CCL8 genes did not lead to clinically significant changes in HBsAg levels or HBV DNA in this study.

Phase I and II studies: Nucleos(t)ide analogues.

Tenofovir Alafenamide (TAF) is an alternate prodrug of tenofovir (TFV) and has been shown to more efficiently deliver TFV to hepatocytes and lymphoid tissue at lower doses than needed with tenofovir DF (TDF). In ongoing phase II studies in HIV patients, TAF showed similar efficacy to TDF with less impact on renal function and bone mineral density. In the current open-label phase Ib study, TAF doses of 8, 25, 40 and 120mg where compared to TDF 300mg for 28 days. The kinetics of serum HBV DNA were comparable among the different dose groups and similar to TDF. There were no significant adverse events, and no subject experienced a renal event. This promising pro-drug will be further developed at a dose of 25mg. Another novel nucleotide analogue, besifovir, which is a acyclic nucleotide phosphonate with a comparable chemical structure to adefovir and TDF, showed non-inferior efficacy to entecavir in 75 Asian, predominantly HBV genotype C infected CHB patients (n=36 besifovir 90mg, n=39 besifovir 180mg daily). Sixty-three percent of patients achieved an undetectable HBV DNA at week 48, while 11-15% achieved HBeAg seroconversion. Importantly, in 94% of patients treated with besifovir a lowering of serum L-carnitine was observed, which normalized with L-carnitine supplements. While NA treatment is generally indefinite with unknown side-effects in the long term, these results for besifovir were definitely not encouraging in terms of safety.

Phase III clinical study: Therapeutic vaccination.

In this trial, 151 HBeAg-positive and HBeAg-negative patients were randomized to either a vaccination regimen, consisting of HBsAg and HBcAg proteins given every 2 weeks intra-nasally 5 times (100 micrograms/dose for 10 weeks) followed by every 2 weekly intra-nasal administration of 100 microgram vaccine combined with 100 microgram subcutaneously (another 10 weeks) (n=75), or to receive

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PEG-IFN α-2b 180 microgram for 48 weeks (n=76). At the end of treatment, 61% of patients receiving therapeutic vaccine versus 67% receiving PEG-IFN achieved an undetectable HBV DNA. For PEG-IFN this percentage dropped to 39% at 24 weeks off-treatment, while a similar rate of patients treated with the therapeutic vaccine remained undetectable. No safety concerns were raised in this study.

Summary

There is a need for new antiviral agents that have the ability to induce sustained off-treatment immune control of HBV. In this regard, the expectations for the TLR-7 agonist were high, but the results of the first human study were definitely disappointing given the fact that no changes were observed in HBV parameters. In contrast, the HBsAg/HBcAg therapeutic vaccination showed favorable off-treatment results when compared to PEG-IFN, and may be a good treatment option in the near future. However further off-treatment follow-up is still ongoing. Of the new agents presented at the 2013 AASLD meeting, the most promising included TAF, as it has a better safety profile compared to TDF, and shows similar efficacy at lower dosing. Nonetheless, it is to be expected that TAF will not induce off-treatment immune control. Given these facts, for more efficacious immune stimulating anti-HBV therapy than that currently available, there is still a long way to go.

Professor Harry L.A. Janssen MD, PhD
Francis Family Chair in Hepatology, Professor of Medicine, University of Toronto & Erasmus University Rotterdam, Head of Hepatology, Toronto Western & General Hospitals, 399 Bathurst Street, 6B FP, Toronto, ON, M5T 2S8 Canada

Email: harry.janssen@uhn.ca

Eradication of hepatitis C virus (HCV): Possibility or fantasy

by Professor Jordan J. Feld MD MPH
Toronto Western Hospital, Toronto, Canada

It is a very rare occurrence that humans have the opportunity to even contemplate the possibility of eradication of a human disease. To date, eradication has only been achieved with small pox, while many attempted eradication programs have failed. There are four essential requirements for eradication of a human infectious disease. There must be no animal or environmental reservoir that could reinfect susceptible humans in the future; there must be a test to identify all infected individuals; a treatment to cure all those infected; and a strategy to prevent all new chronic infections.

Despite its discovery just 25 years ago, the requirements for eradication of hepatitis C virus (HCV) are starting to fall into place. Although recent studies have identified HCV-like viruses in horses, dogs and some small rodents, these viruses are distinct from human HCV and pose very low or no transmission risk to humans. Unfortunately the other tenets required for eradication are not as straightforward.

Since the development of highly sensitive and specific serological and nucleic acid tests for HCV, diagnosis of infected individuals has not posed a technical challenge. However the asymptomatic nature of the disease means that most individuals do not seek medical care for HCV infection until they have very advanced and symptomatic liver disease. In most industrialized countries, fewer than 50% of infected individuals have been diagnosed and this figure is much lower in most developing nations. Efforts to increase screening for HCV in populations with higher disease prevalence will hopefully greatly reduce the number of patients presenting with advanced stage disease. However, only true population screening will identify all infected individuals. Although technically feasible in some regions of the world, widespread population screening is cost prohibitive with current testing methodologies. Programs to develop robust point-of-care diagnostic testing platforms are underway but will need to make great strides before identification of all infected individuals can truly be considered a possibility.

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The most dramatic developments in the field have taken place in the therapeutic arena. From cure rates of less than 10% with poorly tolerated standard interferon monotherapy, we are now on the cusp of therapies with the potential to cure all treated individuals with a single pill taken for as short as a few weeks. It is this dramatic and rapid treatment evolution that has raised the prospect of HCV eradication. Although these treatments will soon be approved for use in many regions of the world, enormous barriers remain before they will be widely accessed by infected individuals. The competitive pharmaceutical industry will recoup its costs and profit enormously with the sale of these novel therapies. Even in many wealthy countries, the prospect of treating all infected individuals is simply not feasible. The costs are too high, the populations are too difficult to reach and in many areas, there are not enough treaters to provide the needed care. For countries with the greatest burden of HCV, largely in the developing world, broad access to treatment is not on the near horizon. However, it is too early to abandon the dream of eradication. Novel approaches will clearly be required. The number of treating physicians can and will expand as treatment algorithms simplify. As occurred with HIV, lobbying governments, charitable organizations and most of all, pharmaceutical companies, will hopefully lead to broader access to currently expensive but effective treatments. Although there will be challenges, diagnosis and treatment of all those infected may not be impossible.

The final challenge is perhaps most daunting. How can all new infections be prevented? Currently HCV is spread predominantly through injection drug use in wealthy countries and through iatrogenic infection in poorer nations. Harm reduction programs and treatment as prevention may markedly reduce transmission in drug-using networks. Reducing the use of unsafe medical practices will be challenging but perhaps not impossible. Healthcare providers in poor countries should not reuse needles. It will take significant financial investment but if safe medical practices can be introduced in developing countries, transmission of not only HCV but all blood-borne pathogens will be greatly reduced and therefore this should be a major priority. However, to truly prevent all new infections from occurring, a vaccine is likely required. The enormous genetic diversity of HCV and the lack of protection provided by spontaneous or treatment-induced viral clearance have made vaccine development a daunting task. With current technology, true sterilizing immunity required for a protective vaccine is not possible. However, the prospect of a vaccine that could greatly increase the rate of spontaneous clearance upon infection appears much more attainable. Early studies are already ongoing with this approach. Unfortunately the recent ban on the use of chimpanzees will further slow down vaccine development.

The fact that HCV eradication is even something to contemplate in 2014 is truly a remarkable achievement. It will take a true global effort to drive the advances in technology, delivery of healthcare, access to medications and social change required to move HCV to the brink of extinction. It is still far from reality but it has moved from fantasy into the realm of possibility.

Professor Jordan Feld MD MPH
Toronto Western Hospital Liver Center
University Health Network
Sandra Rotman Centre for Global Health
Toronto, Canada

Email: jordan.feld@uhn.ca