

Hepatitis B and C Public Policy Association

NEWSLETTER

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An interview with Professor Jean-Michel Pawlotsky on how the treatment of HCV infection will change in the near future as a result of recent developments.

with Professor Jean-Michel Pawlotsky MD, PhD
Director of the French National Reference Center for Viral Hepatitis B, C and delta.

Q: Professor Pawlotsky, could you provide us with a quick overview on how treatment of HCV infection will change in the coming years?

Treatment of hepatitis C will change completely within the next few months and forever. Two drugs will be approved in Europe in February 2014, simeprevir and sofosbuvir. They should be followed by faldaprevir, daclatasvir, ledipasvir and many others, currently at the clinical developmental stage. I see the next two years as a transition period in which interferon/ribavirin-based triple combination therapies will still play an important role. By the end of 2015, they will most likely be replaced by all-oral, interferon-free regimens... if the payers are willing to pay for these expensive new therapies as first-line treatments. There will be schematically three options: a) treatments based on the use of a nucleotide analogue in combination with another drug with a low barrier to resistance, with or without ribavirin; b)

triple combinations of three drugs with a low barrier to resistance (a protease inhibitor, an NS5A inhibitor, and a non-nucleoside inhibitor of the HCV RNA polymerase) with or without ribavirin; c) double combinations based on the use of at least one second-generation protease and/or NS5A inhibitor with or without ribavirin. We will then need to learn how to use these combinations in the real world, which is always trickier than clinical trials.

Q: My feeling by following you on Twitter, is that your biggest fear is that most of these drugs will not be available in some countries. Am I correct?

This is indeed one of my concerns. The drug industry has invested billions of euros in developing these new therapies, and it is understandable that they need a return on investment at some point. However, the financial world has also been very involved in HCV drug development and this has artificially increased development costs and will subsequently oblige the drug industry to sell their drugs at a very high price. It is not absolutely sure that Western European social security systems will be able/willing to afford these costs for all patients, and it is likely that some countries will raise barriers to these therapies. Needless to say emerging countries and the developing world have been left out of new HCV drug development. No access to new drugs through clinical trials in most cases; little hope that affordable new drugs will be available on the short- to mid-term. I recently visited Chile for their national Gastroenterology and Hepatology meeting. Chile is an emerging country with a solid economy and a growth rate of approximately 4-5% per year. They have a highly efficient medical system. In spite of this, Chilean doctors still treat their HCV patients with peginterferon alpha and ribavirin. Their question there is not "shall we be able to use sofosbuvir, simeprevir, and all the other drugs soon?", it is "when will we have access to telaprevir and boceprevir for our patients?", these two drugs that happened to be so toxic and of little help in

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patients with advanced liver disease. This is shocking in a way and we must, collectively, find solutions.

Q: What should hepatologists, scientific societies and patients' associations do to make these drugs rapidly available?

I believe that scientific societies, including national and international societies, if their leadership is strong and has a vision, can be of great help. Guidelines and independence from industry are key tools to move the field forward and have not the power, but the "influence" to make things change. However, I do not overestimate the medical power and in the end, patients' associations, if they are well organized and professional, are the only bodies that can really make things change. Close collaboration between medical societies and patients' associations is therefore key and no major move has taken place over the past years without such collaboration. Finally, the power is in the hands of the drug makers. If they decide, as they did for HIV under strong pressure from powerful activist groups, to make their drugs available at a reasonable cost in developing areas, access to care may be achieved. Only if...

Q: Since you are both a hepatologist and a virologist when do you think we will ultimately be able to eradicate HCV worldwide?

Eradication depends on the tools you have, but also on the political willingness to achieve this goal. It is unlikely that a prophylactic HCV vaccine will be available in the short- to mid-term. Thus, we will have to rely on antiviral therapy. Eradicating an infection by therapy requires three conditions: 1) that the available therapies be highly efficient in curing infection (this will be achieved soon); 2) that access to care be guaranteed to every diagnosed patient; 3) that patients be actively screened for HCV, chronic hepatitis C being silent until liver disease is advanced. The last two requirements are far from being fulfilled, unfortunately. They represent the challenge for tomorrow.

The interview was conducted by
Dr Alessio Aghemo, MD PhD
1st Division of Gastroenterology
Fondazione IRCCS Cà Granda Ospedale Maggiore
Policlinico
University of Milan, Italy

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Professor Jean-Michel Pawlotsky MD, PhD Director of the French National Reference Center for Viral Hepatitis B, C and delta and Chief, Department of Biology
Head, Department of Virology, Bacteriology-Hygiene, and Mycology-Parasitology
Head, Research Team "Pathophysiology and Therapy of Chronic Viral Hepatitis" (INSERM U955) at Hopital Henri Mondor
Universite Paris Est, 51 avenue du Marechal de Lattre de Tassigny 94010 Creteil, France
Email: jean-michel.pawlotsky@hmn.aphp.fr

Epidemiology of Hepatitis C

by Professor Francesco Negro
University Hospitals, Geneva, Switzerland

The recent Viral Hepatitis Congress held in Frankfurt, Germany, from 26th to 27th September 2013, provided the opportunity not only for summarizing the most recent and exciting advances in the therapy of all viral hepatitis, but also for focusing on the issues related to the epidemiology of hepatitis virus infections. My intervention focused on the epidemiology of the hepatitis C virus (HCV), with particular regard to the risk of transmission in various regions of the world and the modalities of its prevention.

Epidemiology is still an important discipline, especially when safe

and effective drugs come at hand. Epidemiology provides a detailed cartography of infection and disease state distribution across different geographical areas of the world. In addition, it identifies the most relevant drivers of such distribution, assessing the relative weight of inputs vs. outputs. These data allow estimation of the current and future public health burden, providing crucial data for policy and action to all stakeholders.

Although several recent estimates of global HCV epidemiology have been published^[1,2], our current appreciation of the HCV pandemic is incomplete. In fact, surveys have been

often conducted in selected groups, excluding high-risk populations such as prison inmates, migrants and other groups living in social exclusion. Furthermore, many surveys in several areas of the world are outdated and have failed to take into consideration the proper extent some recent drivers such as migratory movements, including those composed by war refugees. Finally, one has to recognize that, even when data on prevalence are abundant, those on the disease burden are scanty and incomplete.

HCV infects an approximate 185 million people worldwide, with great variations from one region to another.

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Drivers of HCV infection have changed across the decades. In resource-rich countries, before the introduction of screening assays most infections were iatrogenic, i.e. due to transfusions with infected blood and its derivatives or to unsafe invasive medical procedures. Although before 1990 the risk of transmitting HCV via a blood transfusion was significant (0.45% per unit transfused)^[3], the introduction of screening assays resulted in a decrease in risk to 1 per 1,000,000 units, a merely theoretical risk^[4]. On the other hand, a case-control study from Italy showed how the use of non-disposable needles within or outside the same family bore a significant risk of spreading HCV within closed communities^[5]. Iatrogenic transmission of HCV has since declined dramatically, but some small outbreaks are still reported due to breaches in standard safety procedures, suggesting insufficient awareness within the medical community^[6]. Iatrogenic transmission has played a major role – and unfortunately still does – in resource-limited countries. The most dramatic example is represented by the spread of HCV in Egypt via mass parenteral treatment of Schistosoma infection until the mid 1980's^[7]. Other less famous – but not less devastating – examples that occurred throughout colonial Central Africa have been reported^[8]. Unsafe injections and medical procedures (such as pose of stitches, surgical interventions and gum treatments) are still a scourge in these areas to this day^[9]. Interestingly, a recent paper reported that a small proportion of the rural Egyptian population runs a high risk of HCV infection through frequent medical procedures and injections^[10]. This is sufficient to maintain the high level of spread of HCV infection in that area, and it has been suggested that a targeted intervention in this small proportion of patients may be effective to curb the epidemic in a situation of significant economic constraints^[10].

The second most important cause

of transmission of HCV, widespread throughout the globe, is represented by sharing the paraphernalia used in illicit drug use injections. It has been estimated that up to 10,000,000 active drug users may be anti-HCV-positive^[11]. Despite preventive measures, incidence of HCV in this population remains high, especially among new injectors and prison inmates, and reinfection may occur. Thus, it has been suggested that treatment of HCV in these communities should be aggressive and used as a preventive tool, together with scale up of opiate substitution and needle/syringe exchange programs^[12,13].

Mother-to-infant transmission of HCV is the first cause of HCV infection in developed countries. The average risk is low, i.e. about 4% per birth, with about one third of transmissions occurring in utero, according to several studies. Factors predisposing to transmission are a high maternal viral load – although no threshold has been established –, maternal drug use and an untreated HIV infection. A systematic review of 18 observational studies on 3264 participants showed how no intervention could reduce the risk for mother-to-infant transmission and clearly stated that breastfeeding can be safely carried out^[14].

Heterosexual transmission does not represent a major driver of the HCV epidemic. A recent cross-sectional study on 500 monogamous, heterosexual anti-HIV-negative index cases and their spouses (with an anti-HCV prevalence of 4%), followed for a median duration of sexual activity of 15 years (range 2-52 years), showed that only three couples' HCV RNA sequences were compatible with interspousal transmission, with an incidence rate of 0.07% per year (i.e. 1 per 190,000 sexual contacts)^[15]. In addition, no specific practices were related to HCV positivity among couples. On the other hand, HCV transmission has become a major issue in the HIV-positive homosexual

male community. Here, the incidence of HCV has increased by about 20-fold during the past 15 years, from 0.23 to 4.09 per 100 person-years^[16,17]. Risk factors predisposing to HCV seroconversion include history of inconsistent condom use, past syphilis and unprotected anal intercourse with multiple partners. Reinfection is possible. This community may soon also become the target of a specific program of treatment as prevention.

Finally, a major driver of the HCV epidemic is represented by migratory movements, mostly from countries traditionally characterized by a high endemicity rate to those where HCV is less prevalent. Few studies have been performed on this delicate subject, which however deserves more thorough attention. The proportion of anti-HCV-positive persons among the total infected population in a given country can be as high as 23%, such as in the Netherlands^[18]. Targeted screening programs – possibly extended to other infectious diseases such as hepatitis B – may help to limit the future health burden caused by migration.

Conclusions

HCV is a major global pathogen, and its related public health burden is expected to increase in the next 10-15 years. Since safe and effective drugs are coming to the market shortly, the next challenge will be to identify patients at risk of increased morbidity and mortality due to HCV, to link them to proper care, and to treat them. A better knowledge of the HCV epidemiology and its movers may substantially contribute to an effective control of this troubling pandemic.

Professor Francesco Negro
Divisions of Gastroenterology and
Hepatology and of Clinical Pathology
University Hospitals
Geneva
Email: Francesco.Negro@hcuge.ch

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What's new in HCC

Abstracts from the 2013 AASLD meeting

by Dr Morris Sherman, University of Toronto

Abstract 2091 Flemming et al

Risk prediction of hepatocellular carcinoma in patients with cirrhosis: The ADDRESS-HCC risk model.

Abstract 2149 Yang et al

Risk prediction of hepatocellular carcinoma in patients with cirrhosis: Validation of the ADDRESS-HCC risk model.

One of the new ideas in HCC is the development of a HCC risk score, a score that allows one to predict with a high degree of accuracy who is likely to develop HCC within a defined time period. Several such scores already exist. At this meeting an additional score was presented. The model was developed in 34,932 adults awaiting liver transplantation, and registered with the US liver transplant registry. Using Cox regression methods 6 variables were identified, age, diabetes, race, gender and Child-Pugh score. A score was determined that identified the cut-off level to warrant screening. This score was then validated in a separate cohort of patients at the Mayo Clinic. However, this score cannot be applied to non-transplant patients, who would generally have less severe disease than those on the transplant list for non-HCC indications. Furthermore, for many patients the natural history of their liver disease was cut short by liver transplantation. This may affect the validity and generalizability of the score to patients with cirrhosis not requiring transplant.

Abstract 2085 King et al

Statins are associated with a reduced risk of liver cancer: data from a large prospective cohort study.

It has long been suggested that the use of statins are protective against the development of HCC. This relationship was investigated by a group from Boston. They analyzed two cohorts, 39,634 men enrolled in the health Professional Follow-up Study since 1990, and 96,544 women in the Nurses health Study followed since 1994. Risk factors were sought using Cox regression methods. Regular use of statins was associated with a reduced risk of developing HCC (hazard ratio 0.57, 0.35-0.94 95% CI) risk of developing HCC. This study did not determine or look for other risk factors such as viral hepatitis or other liver disease, and so it cannot be assumed that the reduction in risk will apply to patients with known risk factors or high risk scores.

Abstract 2079 Reig et al

Prospective study of the relationship between progression pattern and survival in patients with hepatocellular carcinoma (HCC). The BCLC rationale for second line trial design and analysis.

Over the past year there have been several phase 3 trials of therapy in HCC that failed, including trials of small molecular inhibitors of signal transduction pathways and a trial of a new method of local ablation.

The reasons for failure of the trials is not entirely clear, and this has implications for future trial design. This was investigated by the group from Barcelona. One of the problems is that surrogate markers of survival in HCC therapy that can be used in phase II studies have not been defined. These include time to progression, tumor response and progression-free survival. The study found that time to progression was a valid surrogate of survival, but only if the pattern of progression is the development of extra-hepatic disease or vascular invasion. This study needs external validation, particularly because one of the two Cox regression analyses had too many variables for the sample size. However, this points the way to more rational design of phase II trials of new agents.

Dr Morris Sherman
Toronto General Hospital
200 Elizabeth Street, Toronto
ON M5G 2C4
Canada
Email: morris.sherman@uhn.on.ca



Access to HCV Treatment in Egypt: a short report

by Professor Gamal Esmat

Director of the Viral Hepatitis Treatment Centres, Ministry of Health, Egypt

In a country like Egypt with the highest worldwide prevalence rates for Hepatitis C Virus (HCV)⁽¹⁾ which infects nearly 15 percent of the total population⁽²⁾, providing access to treatment for this huge number of patients is a great challenge. In 2006, Egypt launched the national control strategy for viral hepatitis that was implemented through a regulatory body which is “*The National Committee for Control of Viral Hepatitis*”. This strategy aimed to address the main obstacles that prevent providing broad access for treatment for those who are candidates for antiviral therapy. A highly specialized network of treatment centres were established in such a way as to have one of these centres located within 100 kilometres of every Egyptian city and village. These centres were set up one at a time reaching the current number of twenty-four. A highly qualified team of specialists which are involved in the care of liver disease patients is available at these units to provide integrated care according to standardized treatment protocols. The other problem initially, was the high costs of the standard of care therapy for HCV patients consisting of combined pegylated interferon and ribavirin therapy. To reach the target of the program by providing antiviral therapy for HCV at a

very reduced cost or free of charge whenever possible, the main challenge was to reduce the high cost of the pegylated interferon. The competition between the two main interferon manufacturers together with the availability of a locally produced biosimilar pegylated interferon helped the negotiations which ended with the provision of the pegylated interferon at gradually lower prices. The current cost of the total 48 weeks of combined interferon and ribavirin therapy stands below 2,000 US dollars. A large portion of those who received the treatment under the program did that for free under the umbrella of the governmental support funds offered by the ministry of health. In a resource-limited country like Egypt, delivering therapy to more than 300,000 patients during six years of the program is to be considered a great achievement. The other benefit of the program is the establishment of well designed infrastructures represented by the treatment centres which will be used for implementing other programs directed at chronic liver disease patients like screening for hepatocellular carcinoma and providing antiviral therapy for patients with hepatitis B virus infection.

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Professor Gamal Esmat, M.D.

Vice President for Graduate Studies and Research, Cairo University.

Professor of Tropical Medicine and Hepatology, Faculty of Medicine, Cairo University.

Email: g_esmat@yahoo.com



The 7th Paris Hepatitis Conference

13th & 14th January 2014

by Professor Patrick Marcellin, President of the 7th Paris Hepatitis Conference

The 7th Paris Hepatitis Conference (PHC) will take place on 13th and 14th January.

PHC was created 10 years ago by Prof. Patrick Marcellin, Chief of the Viral Hepatitis Center in Hôpital Beaujon (Clichy). The meeting is held on behalf of Université Paris Diderot, and Hôpital Beaujon.

The concept of the meeting, focused on the management of patients with viral hepatitis, is to provide the state of the art on the management of patients with hepatitis B and hepatitis C presented by outstanding international experts who will illustrate the most recent data as well as their opinion on their clinical applications.

This year, the meeting will summarize the recent spectacular developments in the management of hepatitis C thanks to the new therapies. Currently, triple therapy with telaprevir or boceprevir induces cure in a high proportion (about 70%) of genotype 1 patients. In 2014, new triple therapies with second generation protease inhibitors or polymerase inhibitors or NS5A inhibitors will become available in some countries. These new treatments represent considerable progress with better efficacy in all HCV genotypes, having better tolerance and shorter

duration. However, these treatments will not be available in the majority of countries. A number of new drugs are being currently developed to further improve efficacy and tolerance.

At present, all clinicians have their eyes turned towards a new exciting track: interferon-free therapy. And this perspective raises an important issue that will be at the heart of our discussions during the PHC 2014: which patients to treat now and how to increase their chances of cure; which patients can wait, taking the future options into account?

Importantly, PHC 2014 will dedicate a full day to address important issues related to hepatitis B. We will discuss the long-term efficacy and tolerance in patients receiving the most potent antivirals available. We will also assess the issue of the usefulness of quantification of HBsAg as a new tool for predicting the severity of the disease and the response to therapy. The optimal management of special populations and difficult situations will be extensively discussed: co-infections, cirrhosis...etc.

As in previous PHCs, interactive discussions and many dedicated working luncheons addressing the management of real-life patients will be privileged. Indeed, the ultimate goal of PHC 2014 is to review the

most recent knowledge and discuss its therapeutic applications with the most experienced experts to provide optimal therapy and the best chance of cure to as many patients as possible, worldwide.

**Professor Patrick Marcellin,
Service d'Hépatologie and Inserm
U481, Hôpital Beaujon,
100 Boulevard del Général Clercy
Clichy Cedex France.
Email: pm51059@gmail.com**

Further information regarding PHC 2014 can be found at the meeting website:

www.aphc.info