Serious gaps in viral hepatitis policies in Europe

An interview with Professor Jeffrey Lazarus
CHIP, Rigshospitalet, University of Copenhagen, Denmark and ISGlobal, Hospital Clinic Barcelona, Spain

Q. Professor Lazarus, does the Hep-CORE Study tell us anything about the trend of viral hepatitis mortality in Europe?

That’s hard to answer actually. Each participating country in the Hep-CORE survey is in a different phase of the viral hepatitis epidemic, and reporting practices and definitions vary. The 2016 Hep-CORE Report doesn’t report on mortality, or prevalence for that matter. What Hep-CORE results do are to serve as an unprecedented analysis of regional and national gaps, clearly showing where there are deficient policies and, by default, what action needs to be taken.

Due to a lack of data, we cannot give any official, comparative trends on mortality rates and this is still a big gap in both the 2012 ECDC surveillance report for hepatitis B and C and the 2016 draft of the WHO European action plan on hepatitis. However, the latter does report that 171,000 people die as a direct result or indirectly of viral hepatitis each year, representing 2% of the total deaths in the WHO European Region. We can say that the prevalence of HBV has been declining steadily (largely due to increased vaccination). And while the data for HCV mortality is not complete enough to determine the trend exactly it should be declining rapidly now in Europe as treatment is expanded. And given that all European member states (actually, all UN member states) have committed to the Sustainable Development Goals and to the WHO Global health sector strategy on viral hepatitis, 2016–2021, I am hopeful that even more rapid progress is on its way. On top of that, the WHO European Regional Committee has approved the Action plan for the health sector response to viral hepatitis, so we can hope for a more coordinated effort in the European region to tackle viral hepatitis.

Q. Do all 27 EU countries have strategies in place to address viral hepatitis B and C?

Well, in our Hep-Core study, we investigated 20 European Union member states. Of those, nine said that they had written national strategies to combat hepatitis C, or hepatitis B, or both. Since just under half of the countries had written strategies, I think we have a long way to go. We hope that the Hep-CORE study, and the WHO action plan will put hepatitis into a spotlight for European decision-makers. And that subsequently the number of EU countries that have strategies to combat viral hepatitis will substantially increase in the coming years.

It is worth noting that unlike for HIV, there is no European Union framework for hepatitis. Such a framework, even combined with HIV and TB, would show leadership in this area and help EU member states address and prioritise viral hepatitis.

Q. What measures should be exploited upfront to meet WHO’s goal of eliminating viral hepatitis B and C by 2030?

We need to recognize that viral hepatitis in Europe is a multi-faceted problem. We’re going to need an equally multifaceted, comprehensive systems approach to tackle it. We now have great direct-acting antivirals for hepatitis C, so from a biomedical perspective curing the infection should not be a problem. The
Gilead’s HCV elimination efforts
John G McHutchison1 Anu Osinusi2 Diana Brainard3
Gilead Sciences Inc, Foster City, CA, USA

Introduction
Hepatitis C virus (HCV) infection is a global health challenge with an estimated 130-150 million individuals infected worldwide [1]. Due to the rapid transformation in the treatment landscape of HCV infection over the last 4 years with the approval of highly effective, safe and tolerable therapies, HCV elimination is now possible.

In 2016, the World Health Organization (WHO) set ambitious but achievable HCV elimination targets with proposed reductions of 60% in HCV-related mortality and 90% in HCV transmission globally by 2030 [2]. This goal of eliminating HCV as a public health threat is predicated on improvements in infection control, scaling up prevention strategies including harm reduction, and increased access to HCV testing and treatment.

Q. What are Gilead’s efforts towards HCV elimination?
The backbone of HCV elimination is the availability of well-tolerated, oral, short duration, directly-acting antiviral (DAA) therapies that are effective across all HCV genotypes. Since the approval of sofosbuvir (SOF, Sovaldi) in 2013, ledipasvir/sofosbuvir (LDV/SOF, Harvoni) in 2014, and sofosbuvir/velpatasvir (SOF/VEL, Epclusa) in 2016, over 1.6 million individuals have been treated with SOF-based therapies across the world [3,4]. Pangenotypic, single tablet regimens with efficacy rates of > 95% across all genotypes and degrees of fibrosis are an essential component of global HCV elimination [5,6]. Ongoing drug development continues to be focused on providing treatment options for all HCV patients including those who have failed multiple prior treatments [7].

Q. What is Gilead doing with regards to HCV elimination in resource limited countries?
Over 70% of the 150 million people infected with HCV live in low to middle-income countries and Gilead is committed to enabling access for all people regardless of where they live or their economic means. Building on efforts in the HIV field, Gilead’s strategies include differential pricing and generic manufacturing licensing. With improved affordability, these agents provide for the first time highly efficacious, safe, and well-tolerated treatment options for HCV-infected patients in low-resource settings where the disease burden is among the highest in the world.

Q. Are there treatment delivery models that could aid elimination efforts?
HCV regimens with favorable safety profiles and pangenotypic activity such as SOF/VEL which do not require dose modification or on-treatment laboratory monitoring will simplify the treatment algorithm, permitting scale up in resource-limited settings. Gilead is involved in two studies to demonstrate the safety and efficacy of this approach. In an ongoing study in India of SOF/VEL for 12 weeks, patients will be evaluated by providers during treatment however on-treatment laboratory tests will not be performed. A similar pilot study (SHARE: Simplifying Hepatitis C Antiviral therapy in Rwanda for Elsewhere in the Developing world) is ongoing in Rwanda where patients will be treated with LDV/SOF and either managed with standard or limited laboratory monitoring. Results from these 2 studies could, if successful, inform future treatment delivery models in global HCV elimination efforts.

Q. Are there nationwide elimination programs that Gilead is supporting?
Gilead is supporting several pilot nationwide elimination programs in low, medium and high HCV prevalence countries. The disease dynamic, burden and characteristics in each country are important to recognize prior to the design of countrywide elimination programs.

In countries such as Iceland with a low prevalence of HCV (0.5%), there are an estimated 1000-1200 individuals with chronic HCV, of which ~ 20-30 were treated annually prior to the availability of sofosbuvir and ledipasvir in 2013. Since then, over 100 individuals have been treated annually with LDV/SOF, and reported adherence to DAA is > 80%.

In countries such as Spain with a high prevalence of HCV (3.5%), over 100,000 individuals are treated annually with LDV/SOF and reported adherence to sofosbuvir is > 80%

In countries such as Iceland and Spain, Gilead is committed to enabling access for all people regardless of where they live or their economic means. Building on efforts in the HIV field, Gilead’s strategies include differential pricing and generic manufacturing licensing. With improved affordability, these agents provide for the first time highly efficacious, safe, and well-tolerated treatment options for HCV-infected patients in low-resource settings where the disease burden is among the highest in the world.
of DAAs. Iceland represents an ideal setting to test the concept of nationwide elimination due to the low prevalence infected population, “closed system” with limited migration and strong health care infrastructure that tracks all new infections and allows easy access to treatment, including high risk groups. Gilead is supporting the nationwide elimination effort by providing medication to treat all HCV patients according to Icelandic guidelines over the next 3 years. To measure the effect of this nationwide treatment program, the incidence of HCV infection acquired in Iceland and the rates of cirrhosis and hepatocellular carcinoma due to HCV will be monitored for up to 15 years.

In April 2015, Georgia which has a high HCV prevalence of 7% embarked on the world’s first elimination program in partnership with Gilead, CDC, WHO and others [8]. The initial phase of the program focused on providing HCV treatment to infected persons with advanced liver disease and at highest risk for HCV-associated morbidity and mortality. Since May 2015, over 9000 patients have been treated with SOF based therapies. The next steps in this comprehensive HCV elimination plan include implementation of infection control measures, prevention initiatives, enhanced screening and linkage to care, with the goal of reaching HCV elimination by 2020.

Gilead is also supporting several key initiatives in Australia that are part of its nationwide elimination program.

Q. What about treatment as prevention?

The availability of highly effective treatment with low rates of adverse events has brought into focus the concept of using treatment as prevention (TraP) and thus close to eliminating transmission of HCV infections in a single group. In high-income countries, people who inject drugs (PWID) and prisoners are among the groups at greatest risk of HCV infection [9]. If HCV treatment can be delivered effectively to high-risk transmitters and social networks, significant reductions in the incidence of HCV cases are possible. Gilead is supporting the TAP (Treatment as Prevention) study in Australia which is investigating the feasibility of treating PWIDs in a community based setting. It will also measure the effectiveness of using a social network-based approach (“bring your friends”) to reduce HCV incidence in PWID.

Another setting that provides opportunity to assess the feasibility of HCV treatment as prevention is in correctional centers. In Australia and many other countries, almost half of all prisoners report injecting drug use with the majority eventually released back into the community [10]. To this end, correctional centers represent a significant public health opportunity to assess the feasibility of HCV treatment as prevention with the aim of reducing the spread of HCV in both the correctional setting and broader community. Gilead is supporting the STOP-C study (Surveillance and Treatment of prisoners with Hepatitis C) in 2 maximum security and 2-4 medium security correctional centers in Australia. This study is in 4 phases including a) Surveillance of HCV incidence and prevalence and liver disease burden b) modeling c) treatment intervention with SOF/VEL and d) cost effectiveness analysis.

In summary, Gilead is committed to developing safe, well-tolerated and highly effective treatment for all HCV infected patients globally and supports numerous important initiatives aimed at addressing HCV elimination projects in communities across the world.

References


John G. McHutchison
Gilead Sciences Inc,
Foster City,
CA, USA
E-mail: john.mchutchison@gilead.com
Hepatitis C in India

Radha, K. Dhiman, MD, DM, FACMS, FACC, FRCP Edin, FRCP London, FAASLD

Gagandeep Singh Grover, MD1 Pankaj Puri, MD, DNB, DM2 Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India,

1Program Officer, Hepatitis C Virus Infection, Punjab and 2Department of Internal Medicine, Armed Forces Medical College, Pune, 411040, India

Professor Dihman, what is the burden of HCV in India?

There is paucity of good quality epidemiological data of the prevalence of HCV in India. Considering 1 to 1.5% prevalence of HCV antibody in India, approximately 12-18 million people are thought to expose to HCV in India. [1] The estimated viremic rate of about 70% corresponds to a viremic prevalence of about 0.84 to 1.26%. [1,2]

The Indian National Association for Study of the Liver (INASL) had reviewed the available data of studies of HCV in India. There is significant geographic variation of prevalence of HCV across various regions of India. The prevalence is higher in the northeastern regions, Punjab and tribal populations, while it is lower in Western and Eastern India. [3]

Population based surveys of prevalence of HCV in India are scarce. Chowdhury et al [4] reported HCV prevalence of 0.87% in a rural Birbhum district of the state of West Bengal. Sachdeva et al [5] found a HCV prevalence of 1.0% in Fatehabad district of the state of Haryana. They also screened 7114 high-risk individuals (with high risk behavior/ history of jaundice), in whom the prevalence was 2.1%. In contrast, very high prevalence has been reported from the population of Punjab, India. Sood et al [6] Multanpur of the state of Punjab, India reported a HCV prevalence of 5.2% with the highest prevalence in the 40-60 years age group. A recent study of HCV in Punjab, India by the same group carried out this year in 5,526 subjects found a prevalence of 8.8% in Hoshiarpur district to as high as 8.8% in 5,526 subjects found a prevalence of HCV by the same group carried out this year. A recent study of HCV in Punjab, India reported a HCV prevalence of 1.0% in Fatehabad district of the state of Haryana. They also screened 7114 high-risk individuals (with high risk behavior/ history of jaundice), in whom the prevalence was 2.1%. In contrast, very high prevalence has been reported from the population of Punjab, India. Sood et al [6] Multanpur of the state of Punjab, India reported a HCV prevalence of 5.2% with the highest prevalence in the 40-60 years age group. A recent study of HCV in Punjab, India by the same group carried out this year in 5,526 subjects found a prevalence of 8.8% in Hoshiarpur district to as high as 8.8%.

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The predominant modes of transmission of HCV in India are unsafe therapeutic injections and blood transfusion; IV drug use is not as widespread in India. [4] In India, injections are indiscriminately prescribed for self-limiting illnesses. Illiterate patients often demand injections with the belief that injections to be more efficacious than oral medication. It is estimated that 3.0 billion injections are administered annually in India, of which approximately 1.89 billion are unsafe due to inadequate sterilization, faulty techniques or inappropriate disposal of injection waste. [12]

The prevalence of HCV in HIV infected individuals varies markedly as per the route of transmission of HIV. Unlike the west, heterosexual transmission of HIV is commoner than transmission by IV drug usage. Globally, the overall prevalence of HCV infection in HIV is approximately 30%. [13,14,15] However, the prevalence of HCV in HIV-infected persons in India is reported between 1.3% and 8.3%. [4,16,17,19] The prevalence of HCV and HIV co-infection in IV drug users has been found to range from 13.2% to 86% in India. [2,19,20,21,22] India is estimated to have approximately 1.1 million IV drug users with HIV prevalence as high as 64% in certain cities. [23] A high number of IV drug users have been found in the northeastern states of Manipur, Nagaland and Mizoram, [24] and from the states in Punjab, Haryana and Chandigarh. [25] While in most states, HCV is prevalent in half to one-third of the IV drug users, a very high prevalence of HCV has been reported from the northeast. [4]

Barua et al [26] found HCV infection in 9.6% of female sex workers. However, in a survey of men who have sex with men in Tamil Nadu, HCV infection was uncommon. [27] Solomon et al [28] also found that heterosexual transmission of HCV is infrequent.

Closed community marriage, cultural practices such as tattooing, traditional therapy including bloodletting and rituals like scarification/branding may explain the higher prevalence of HCV in tribal communities.

Is the genotype distribution of HCV in India peculiar?

Yes, the predominant genotype in India is genotype 3, which is seen in 54% - 80% of cases. In Southern India, both Genotype 1 and Genotype 3 are prevalent. [29] Genotype 4 has been reported from Southern and Western India [30,31,32] and Genotype 6 infection was initially reported in two cases from Eastern India. [33] A study in the tribal dominant part of the northeast by Medhi et al [34] in contrast found genotype 4 (30.8%) to be the commonest genotype in that region while genotype 6 was seen in 13.6% of 75 isolates. There are two cases of genotype 5a reported from India. [4,35] A recent study done by Sood et al, in 2016 where in genotype 3 was the commonest genotype (55.7%) followed by 1 (28.2%) and 4 (10.1%) (Professor Ajt Sood 2016, personal communication).

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What about the natural history of HCV?

Genotype 3, predominant genotype in the Indian subcontinent, is associated with accelerated fibrosis compared to other genotypes. As compared to the white population, persons migrating from the Indian subcontinent to the United Kingdom were more likely to be older, female, infected with genotype 3 and to not consume alcohol. The Asian patients had higher fibrosis scores, necro-inflammatory scores and steatosis.

There is acceleration of the disease after the age of 40 years. The median rate of fibrosis progression in Indian patients with chronic HCV infection has been reported to be 0.25 (0.0–1.5) fibrosis units per year, which suggests that it would take approximately 16 years for cirrhosis to develop.

How is HCV treated in India?

In India, pegylated interferon alfa (Peg-IFNα) plus ribavirin (RBV) combination therapy has been replaced by directly acting antiviral agents (DAAs). DAA have lower side effects, better tolerability, and are simpler to administer. The nucleoside non-structural protein Non-structural (NS) 5B inhibitor sofosbuvir (SOF) became available in India in March 2015, which was followed in 2016 by the NSSAI replication complex inhibitors, ledipasvir (LDV) and daclatasvir (DCV). Velpatasvir (VEL), a pan-genotypic DAA, is likely to be soon available in India and the Indian National Association for Study of the Liver (INASL) guidelines are accordingly going to be updated. The INASL has periodically updated guidance on therapy of HCV in India corresponding to the drug availability. The INASL guidelines are based on considerations for the treatment of HCV in India including the cost of therapy, the poorer response of the predominant genotype (genotype 3) and the non-availability of many of the DAA recommended by other guidelines. The widespread uptake of DAA in India is possible, as these have so far been marketed at a fraction of the cost in the west. Preliminary reports of the generic DAA have shown reasonable results (Table).

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viral response (SVR 12). HCV core-Ag may be a useful alternative to HCV RNA testing in resource-constrained settings and can be done by smaller laboratories where HCV RNA testing may not be feasible. [46] If there is no clinical or ultrasound evidence of cirrhosis, genotype testing could be avoided and patients can be treated with the pangenotypic combination of DCV/SOF. [46] Punjab has an overall hepatitis-C prevalence of 3.29%, with rural prevalence as 3.4% and urban as 3.1%. Using the above prevalence estimates, more than 9 lakhs citizens are estimated to be infected with Hepatitis-C, of which ~6 lakhs are expected to be viraemic and will require treatment. With the growing cognizance of the HCV burden in the state, the Government of Punjab launched a public health program under the Mukh Mantri Punjab Hepatitis-C Relief Fund (MMPHCRF) that offers free hepatitis-C treatment to all residents of Punjab through a highly decentralized network of 22 District Hospitals and 3 Government Medical Colleges. [46] Considering the pangenotypic efficacy of DCV/SOF therapy, it is considered as first-line therapy for all non-cirrhotic patients without genotype testing and end of the treatment viral load. Patients with cirrhosis are managed according to their genotypes (i.e. DCV/SOF and RBV for genotype 3 and LDV/SOF and RBV for genotypes 1 and 4) (Figure). This approach has been proven to be most cost effective (less than US $ 150 for 12 weeks therapy for genotype 3 patients). The overall results with generics were 93.3% (See Table).

Do you foresee HCV elimination by 2030 to be possible in India?

It has been estimated that only 0.2% of the HCV infected population in India received therapy. [47] Lack of public awareness is a significant barrier to prevention of spread of the disease and early detection. Moreover, poor knowledge in healthcare providers adds to the delay in early diagnosis and appropriate therapy. The cost of therapy and the investigations, while a fraction of that in the West, continues to be prohibitive to many patients. It was shown that while prevention of HCV decreased the overall prevalence, it did not impact the short term liver related mortality or development of hepatocellular carcinoma in India.

Instead, a dual approach of decreasing the incidence of new cases and treatment of old cases was likely to play a vital role in lowering the burden of the disease. [48] The huge burden of HCV in India makes it imperative to implement strategies for control and management of HCV in India. The various stakeholders in the management and control of HCV include the doctors, the government, the non-governmental organizations and the drug companies and all of them have roles to play. At the government level, there is a need to improve the public health and clinical care for prevention of HCV and for improved diagnosis and treatment of HCV. A strict audit of blood banking practices is required to prevent transmission of the disease. There is a need for health education programs for the public and by programs to improve the knowledge of healthcare providers. The educational programs for the healthcare providers should incorporate all the aspects of prevention, care and treatment, which should target multiple levels of health care providers including specialists, family physicians and paramedical staff.

There are few government initiatives like the HCV elimination project launched by the Punjab, state government for case detection health education and management of cases of HCV. However, there needs to be a wider provision for state funding for public health education, diagnosis, screening and provision for free treatment. The doctors have to be actively involved in education of health care workers as well as the public. Safe injection practices have to be universally used by healthcare workers. The drug companies have a role in continuing to provide the newer DAA at realistic rates. The healthcare community is eagerly waiting to know the anticipated cost of VEL, the newer DAA soon to be launched in the Indian market. The non-governmental organizations also have an important role to play. They can supplement the health education programs, provide financial support for therapy and contribute to provision of cheap generic DAA in the Indian market. Despite a low to moderate prevalence of HCV, India contributes significantly towards the global HCV burden due to the large population. Large population-based studies of prevalence of HCV are needed to have a more accurate assessment of the burden of the disease and to identify high prevalence areas where preventive measures can be focused. Only a small fraction of HCV infected persons in India receive therapy. A combined role of preventive strategies and improving access to therapy are required to control the burden of disease in India.

References


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Dr Freeman, what is the rationale for importing generic hepatitis C medications?

In a breakthrough that rivals the invention of penicillin, drugs that cure hepatitis C, with minimal side effects and high success rates, have reached the market, but, in what must be one of the greatest tragedies of modern times, these life-saving medications are not being deployed on a mass scale. Despite the fact a cure now exists, the vast majority of the 150 million patients who could benefit won’t benefit, because our health systems simply cannot afford to pay the extraordinary prices.

Should strategies for hepatitis C elimination mimic what was done for HIV?

This is not the first time the world has seen such a situation. At the turn of the 21st century, when the cost per patient of one year’s HIV treatment was over $10,000, Dr Yusuf Hamied, chairman of the Indian drug giant Cipla, electrified the global health community when he said he would produce HIV medicines for $1 per day [1]. At the time, India did not have a pharmaceutical patent system and, although some viewed his actions as akin to piracy, it was legal [2]. In 2004 a study funded by MSF and conducted in Cameroon was published in the Lancet demonstrating that generic HIV medications delivered the same clinical results as the originator brands [3]. This three-part combination of availability of high quality generic medications, affordable prices, and clinical proof has since seen the number of patients receiving treatment increase from 1% to nearly 50% of all the patients worldwide afflicted with HIV [4].

This historical observation raises the question “Could something similar be done today with HCV DAA medications?” Pharmaceutical patents are gifted to private corporations by governments...
for the dual purposes of protecting R&D expenditure and encouraging innovation. Unfortunately, the monopoly pricing power these patents provision currently lacks adequate checks and balances, is open to abuse, and is quite clearly being abused. The sort of legislative changes required to deliver on the original goals of pharmaceutical patents will take years or even decades to eventuate. Although the geopolitical landscape has changed, for example India now has drug patent laws [8], I believe it remains possible to repeat the success seen in improving access to HIV medications by using parallel importation of HCV generics as the tool to apply market forces to excessive prices.

What about your personal experience with generic medications for hepatitis C?

In medicine “primum non nocere” – first do no harm – remains a guiding principle. My initial involvement with generics was not as an advocate. It happened in February 2014 when a patient said “I am going to do this, with or without you, so will you help?” At this stage, the logic for helping was simple in that good medicine dictated helping minimize the risks so I arranged for testing of the medication and on treatment monitoring. This, to me, was entirely different from actively suggesting the use of generics, which carries a far greater responsibility. In routine medicine we write words on a paper prescription and depend on a complex well-oiled machine to safely deliver the correct chemicals into our patient. To advocate for generics means having confidence that generics can be reliably and safely sourced, and that the medications themselves are safe. So, are generic HCV DAA medications safe?

Are generic medicines involved in issues of safety and effectiveness?

It is fair to say that the quality of generic medications can reasonably be expected to vary. Fortunately, we have well proven systems, which provide quality assurance. These include Bioequivalence, cGMP, ISO, and FDA certifications and WHO prequalification as well as originator licensing and technology transfer. Pharma in Egypt appears likely to be the first generic manufacturer to achieve WHO prequalification and manufacturers like Cipla, Hetero and Mylan in India have previously proven their capability to meet all these requirements for HIV generics [8]. I have personally seen the bioequivalence data from several manufacturers and will be presenting some at this year’s EASL ILC in Amsterdam.

Generic versions of the DAAs are manufactured in many countries according to their local rules and regulations. We observe 3 models: Egypt has no patent on sofosbuvir [6] and Raymond Schinazi helped them set up production; Bangladesh is not required under the WTO TRIPS arrangements to respect patents [7]; and in India Gilead has licensed a number of manufacturers to manufacture DAAs for sale within a restricted set of territories [8].

Is there a way to circumvent restrictions to access to generic hepatitis C medicines?

While each country provides a potential source of generics I will use the Indian model as the example case because it is the most complex. Under Indian licensing arrangements, the wording is not that of an end user license, such as might be seen for arms sales, instead it restricts sales to within certain territories [8]. With this in mind, at FixHepC we reasoned that if an invoice is issued in India, and there has been a Telehealth consultation with an Indian doctor generating an Indian prescription then the sale of the medication occurred within a licensed territory, namely India. The fact that this medication then happens to fall into a FedEx courier satchel is immaterial. Having legally exited the country of origin we now arrive at customs in the destination country. Article 60 of the WTO TRIPS agreement is called “de minimus imports” and makes small shipments exempt from patent-related import/export restrictions [10]. In line with this most countries provision a citizen’s right to import 3 months medication for their own use, indeed Swissmedic have just adjusted their previous 1 month limit to 3 months to facilitate this process [11]. While this process might be viewed to violate the spirit of the law, it does not violate the letter of the law. More details on this can be found in my Liver International article “The use of generic medications for hepatitis C” [12].

What is the global therapeutic role of generic HCV medications?

It is interesting to note that Egypt has treated over 1,000,000 patients with generic HCV medications with excellent results [13]. This approximates the entire number of patients that have been treated worldwide with originator brands. When we add in the contribution from India, Bangladesh and other countries generics are already the major source of HCV cure worldwide.

Dr Freeman, why was your pioneer study REDEMPTION a real breakthrough?

The REDEMPTION generics trial was initiated when my initial single patient had become 20 by word of mouth and it occurred to me that at least one of these patients would fail treatment, so it would be wise if I could explicitly prove that the number of failures were in line with expectations. Although the structure of the trial is unusual with geographically distributed patients paying for their own medication the key points are that it recruited and monitored 448 consecutive patients and the absence of exclusion criteria provided a representative and real world sample.
REDEMPTION was initially reported at EASL ILC 2016 [14] and again at AASLD 2016 [15]. The final results will be presented at EASL ILC in 2017 in the abstract entitled PS-097: Sustained virological response for 94% of people treated with low-cost, legally imported generic direct-acting antivirals for hepatitis C: Analysis of 1087 patients in 4 treatment programmes. The consistent results delivered by generic products, across diverse genotypic, ethnic and geographic regions is reassuring.

Doctors prescribing and monitoring patients taking generics can take comfort from the fact that the REDEMPTION trial results show [14,15], like the HIV generics that came before them [3], that HCV generics deliver robust clinical results.

In November 2016 an excellent overview article was published in the Lancet called “Importation of generic hepatitis C medications from Beacon, Incepta, Cipla, Hetero and Mylan and others. 

Dr J. Freeman assists patients in obtaining access to generic hepatitis C medication via the http://fixhepc.com website and has received subsidized travel from Beacon Pharmaceuticals and Pharco Pharmaceuticals. He has independently tested generic medications from Beacon, Incepta, Cipla, Hetero and Mylan and others.

Disclosure

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References


An interview with Dr. Marc Boulière MD PhD, on the clinical impact of resistance to hepatitis C DAAs

Marc Boulière, MD PhD,
Head of Hepato-Gastroenterology Department, Hôpital Saint-Joseph, Marseille, France.

Q. Dr Bourlière, how many naïve patients with HCV circulate DAA resistant virions? Have predictors of resistance been identified in these patients?

Data about the prevalence of resistant virions in DAAs naïve patients are heterogeneous biased partly by the different techniques used (population or deep sequencing) and partly due to the method used to study resistance-associated substitutions (RASs) (some studies reported all RASs or others reported only RASs that confer proven resistance in vitro resistance), and in most studies there is an absence of linkage. Moreover most of the data have been reported on genotype 1 patients [1,2].

NS5B RASs are rarely detected at baseline and therefore have no impact on SVR irrespective of sofosbuvir-based combinations used [3].

NS3 protease RASs can be detected at baseline. Many RASs are associated with replicative impairments that explain a relatively low likelihood of detectable pre-existence as well as a rapid replacement by wild type virus [4]. The natural occurrence of single RASs in HCV genotype 1 patients is between 0.1 and 3.1%. The exception is the Q80K variant, which has no loss of replicative fitness and has relatively high probability of pre-existence. This variant is mainly detected in genotype 1a patients with important geographical differences, 48% in USA and 19% and 9% in Europe and South America, respectively. The Q80K variant is associated with different levels of resistance for the approved NS3 protease inhibitors. The presence of Q80K mutations induced reduces SVR with sofosbuvir/velpatasvir combination for 12 weeks in genotype 1a patients with cirrhosis and prior failure to pegIFN and ribavirin (PR). By contrast, Q80K mutation does not influence SVR in genotype 1a patients treated with paritaprevir/ritonavir/ombitasvir plus dasabuvir (PRD) and ribavirin or asunaprevir/daclatasvir or grazoprevir/elasvir.

NSA RASs are often detected at baseline in DAA naïve patients, between 15% and 27% according to geographical variations using a method with 1% cut-off [5]. The effect of baseline NSA RASs varies according to the DAAs combination used. For sofosbuvir/ledipasvir combination, baseline NSA RASs do not impact SVR except in a small group of genotype 1a patients with cirrhosis and previous failure to PR. Moreover, addition of ribavirin appears to reduce the effect of pre-existing NSA RASs. For the pangenotypic regimen sofosbuvir/daclatasvir, NSA RASs have no impact on SVR except in genotype 3 patients with cirrhosis. Whether SVR can be improved by addition of ribavirin or extension of treatment duration still remains unclear but is suggested by one study (ALLY3+) [5]. For the pangenotypic single pill combination sofosbuvir/velpatasvir, NSA RASs have no impact on SVR except in genotype 3 patients with cirrhosis. Whether SVR can be improved by addition of ribavirin or extension of treatment duration still remains unclear but is suggested by one study (ALLY3+) [5]. For the pangenotypic single pill combination sofosbuvir/velpatasvir, NSA RASs have no impact on SVR except in genotype 3 patients with cirrhosis. Whether SVR can be improved by addition of ribavirin or extension of treatment duration still remains unclear but is suggested by one study (ALLY3+) [5].

NSRA RASs have a substantial impact on SVR after 12 weeks of grazoprevir/elasvir without ribavirin in genotype 1a patients and in genotype 1b patients non-responders to previous PR regimen. This effect disappears if ribavirin is added and treatment duration is extended to 16 weeks.

Baseline mutations at position 31 and 93 negatively impact SVR in genotype 1 patients treated with asunaprevir and daclatasvir and this combination should be avoided.

Overall, pre-existing RASs in naïve patients are not a major issue if patients are treated according to the guidelines. There is no need for pre-treatment assessment of HCV RASs. There are no host factors so far, that are predictors of resistance, and occurrence of resistance after DAAs is highly related to the combination used and more frequent when DAAs with a lower barrier of resistance are used. That is why NS3B nucleotide acts as a backbone for antiviral combination.

Resistance of HCV to DAAs is determined by three major factors: the first one is the genetic barrier to resistance, related to the number and type of nucleotide substitutions required for the emergence of RASs during replication and to the number and types of RASs required for a viral variant to acquire full resistance to the drug. The genetic barrier to resistance varies with drug class, specific drug and HCV genotype or subtype (1a vs 1b). It determines the likelihood that resistant viruses are generated during replication. The second factor is the fitness of resistant virus population that is independent of the level of resistance conferred by the RASs. Fitness determines the likelihood that resistant virus persist in minor or major population. Finally, the last factor is the level of drug exposure necessary to inhibit replication of resistant variants.

Q. Are RASs involved in DAA treatment failures and if so, can we identify patients at risk?

In adherent patients, virological breakthroughs are rare and most treatment failures are relapses. At treatment failure, a large proportion of...
patients harbors either NS3 or NS5A RASs unless treatments have been too short to clear wild type virus and in this case this virus may be predominant. Patients at risk of viral failure are those with advanced disease (compensated or decompensated cirrhosis) and especially patients with genotype 3 and less frequently genotype 1a.

Resistant variants after treatment failure have a different impact on retreatment according to the drug class. Sofosbuvir-resistant variants are rare and poorly fit and rapidly disappear after relapse. They do not affect sofosbuvir-based retreatment. NS3-4A RASs rapidly disappear within a few months after treatment withdrawal. It is not yet clear whether the occurrence of these RASs even if they disappeared, affect retreatment with NS3-4A protease inhibitors-containing regimen. On the contrary, NS5A RASs are long-lasting, remains dominant species for several years and may likely affect the results of retreatment.

Q. How can we prevent and treat RASs associated with treatment failure?

Simple rules in accordance with the guidelines can be used to optimize treatment and avoid virological failure. In patients with cirrhosis, the guidelines recommend adding ribavirin to 12 weeks of treatment with sofosbuvir/ledipasvir, sofosbuvir plus daclatasvir or sofosbuvir plus simprevir or to prolong therapy up to 24 weeks in order to reduce relapses. Genotype 1a cirrhotic patients treated with PROD should be treated for 24 weeks with ribavirin and patients without cirrhosis should be treated 12 weeks with ribavirin. For grazoprevir/elbasvir, genotype 1a patients and genotype1b patients non responders to PR may be treated for 16 weeks with ribavirin without pre-treatment resistance test, making this regimen more widely accessible. Genotype 2 patients with cirrhosis need to be treated 24 weeks with sofosbuvir plus ribavirin or combination of sofosbuvir/daclatasvir. In the near future, those patients will be treated 12 weeks with sofosbuvir/velpatasvir. Genotype 3 with cirrhosis either compensated or decompensated needs to receive currently either 12 weeks of sofosbuvir/daclatasvir plus ribavirin or 24 weeks of treatment and in the near future sofosbuvir/velpatasvir for 12 weeks will be the option and addition of ribavirin will be necessary only in decompensated cirrhotic patients.

Resistance testing is hard to perform due to the lack of standardized assays available. Population or deep sequencing with in-house techniques are available in a limited number of laboratories in Europe and in the USA. Resistance testing should not be done at treatment failure but may be of interest before retreating patients who failed DAA-based therapy in order to discuss retreatment options.

The retreatment regimen should contain sofosbuvir because of the high barrier to resistance in combination with 1 to 3 other DAs, with no cross-resistance with DAs already administered, with or without ribavirin for 12 or 24 weeks. Addition of ribavirin and longer duration are recommended in patients with factor characteristics of poor response such as cirrhosis [7].

Using this recommendation, retreatment in real-world experience demonstrates high rate of SVR. For those with multiple RASs against PI and NS5A inhibitors retreatment with the current available drug should be cautious due to poor SVR results especially in those with advanced disease. Inclusion in a controlled trial with new combinations is therefore recommended. In phase II trial, retreatment of DAs failure patients with single or multiple RASs with either sofosbuvir/velpatasvir/voxilaprevir or glecaprevir (ABT-493)/pibrentasvir (ABT-530) for 12 weeks achieved SVR in almost all patients. If these results are confirmed in phase III trials the resistance and retreatment issues will be largely resolved.

Dr Marc Bourlière MD PhD
Chef de Service
Hôpital Saint-Joseph, Marseille, France
Email: mbouriere@hopital-saint-joseph.fr

References