A New Era for Hepatitis C—New Diagnostics Tools and New Weapons

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In May, 2011, the FDA approved boceprevir and telaprevir as treatments for chronic hepatitis C virus (HCV) infection. These two small molecules are competitive inhibitors of the NS3 viral protease. Their administration along with peginterferon-α plus ribavirin (triple therapy) has heralded a new era in hepatitis C that somewhat resembles what happened in the year 1996 in the AIDS field, following the approval of the first HIV protease inhibitors and the implementation of combination therapy.

Triple combination therapy for hepatitis C, including any of the first two direct-acting antivirals (DAA), is currently the recommended therapy for patients with chronic hepatitis C infected with HCV genotype 1. In comparison with prior treatment (peginterferon-α plus ribavirin), response rates have increased overall from 35 to 70%, and the length of therapy has been shortened in most subjects from 12 to 6 months. The downside is that triple therapy for hepatitis C significantly increases pill burden and side effects. Moreover, drug interactions and complicated treatment schedules require significant expertise by care providers. Finally, these drugs are quite expensive, and hepatitis C cure is becoming somewhat a privilege for wealthy societies and/or individuals.

Having now the opportunity to cure most patients has sped the interest for treating chronic hepatitis C. However, it has unveiled important gaps that must be filled properly if we want recent advances in therapeutics to translate into significant public health benefits. Whereas HCV has surpassed HIV in mortality rate in the United States (15000 vs 13000 deaths per year), more than half of chronic hepatitis C patients have not been diagnosed yet. This is largely due to the fact that patients with decompensated liver disease only represent a fraction (<10%) of the whole population chronically infected with HCV. In the United States, 2.7 and 3.9 million people (1.3–1.9% of general population) have chronic hepatitis C.[1] Another factor that contributes to the high rate of underdiagnosed HCV is the lack of identifiable risk factors for infection in more than half of cases (they are called "sporadic"). This is in contrast with HIV, for which prior risk behaviors are acknowledged by most infected persons.

The good news on HCV is that new infections have declined over the last two decades, following the introduction of HCV antibody screening tests. Even so, in the United States still, 18000 new HCV infections occur per year. As a comparison, there are 50000 new HIV infections yearly, which overall affects 1.2 million (0.5% of the U.S. population).

Advances in therapeutics have concurred with the arrival of new technologies and diagnostic tools for hepatitis C. Two major breakthroughs for hepatitis C management merit particular recognition. Liver biopsies are no longer required for assessing the severity of hepatic damage caused by HCV.

Noninvasive tools, including serum fibrosis indexes and specially elastometry (FibroScan) now allow rapid, cheap, and accurate assessment of the extent of liver fibrosis in a given patient. In contrast with liver biopsies, these procedures can be performed periodically. Prioritization of treatment in subjects with significant or advanced liver fibrosis seems justified. However, as therapies for hepatitis C would become simpler and cheaper, no doubt most if not all patients will be considered as candidates for treatment, regardless of liver fibrosis stage. Another landmark discovery in hepatitis C comes from genetics. Polymorphisms at IL28B largely influence treatment responses, highlighting the role of the innate immune response in the clearance of HCV.[2]

Personalized medicine is expected to be more prevalent in the near future, with genotypic screening to precede drug treatment.[3] Individualization of therapy in hepatitis C will move on soon testing several gene polymorphisms, as part of baseline assessment and once in life for every patient, using microarrays. Treatment decisions will then be based on genetic profiles, including IL28B, ITPA, ENT-2, UGT 1A1, CYP 3A4, LDLr, and HLA DQ*0301.

The current armamentarium against HCV will soon be expanded with molecules belonging to different drug families, including NS3 protease inhibitors, NS5B polymerase inhibitors [either nucleos(t)ide or non-nucleoside analogues], and NS5A inhibitors. More than 10 drugs are currently completing phase II–III trials (see Table 1), some of which are testing

Table 1. Direct-Acting Antivirals for HCV in Most Advanced Phase II–III Trials

protease inhibitors	nucleos(t)ide analogues	non-nucleoside polymerase inhibitors	NS5A inhibitors
Boceprevir	GS-7977	ABT-333	Daclatasvir
Telaprevir	Mericitabine	BI-7127	
Simeprevir	IDX-184		
BI-1335			
ABT-450/r			
Danoprevir/r			
Asunaprevir			
GS-9256			

experimental regimens with and without interferon and/or ribavirin. No doubt oral regimens taking off subcutaneous peginterferon-α are the most promising, once the proof-of-concept has already shown that they can effectively eliminate HCV. Some combinations should initially be preferred over others. At this time, it looks like nucleotide analogues plus

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either protease inhibitors or NS5A inhibitors are the most attractive. However, several new questions have arisen using interferon-sparing regimens, being among the most intriguing the recognition of rare but confirmed late HCV relapses, occurring beyond 24 weeks after discontinuation of therapy. Other questions that must be answered as oral combination regimens move forward are the following: (i) Why do subtype 1b viruses tend to respond better than subtype 1a? (ii) Which is the shortest successful length of therapy (12, 16, or 24 weeks)? (iii) Should ribavirin be kept on board? (iv) To what extent may innate immunity (i.e., *IL28B* polymorphisms) influence DAA response?

Several public health implications of a rapid and wide use of DAA can be advanced (see Table 2). First, constraints in cost

Table 2. Public Health Implications of the Widespread Use of DAA

1. Significant increments in cost and demands for the health system, including well-trained personnel
2. Reduced needs for hepatic decompensation events and liver transplantation
3. Selection of HCV drug resistance in nonresponders
4. Shift in HCV care providers—more infectologists over hepatologists
5. Marginalization of HCV populations

and availability of well-trained personnel will limit the use of new hepatitis C drugs. Second, the benefit of the new HCV therapies in terms of reduced liver decompensation episodes and the need for liver transplantation will be significant but only after several years. Third, selection of drug resistance in HCV in patients treated with most of the new drugs will require the design of second-line or rescue regimens, as cross-resistance might jeopardize the success of recycling drugs within the same family. Four, a shift in care providers should be expected, with more involvement of Infectious Diseases specialists over hepatologists, due to the new way hepatitis C is managed, targeting asymptomatic infected individuals instead of end-stage liver disease patients and taking decisions based on virological concepts, more familiar for infectologists than hepatologists. Finally, because of economic constraints and access to health care, a shift in HCV populations will occur, with marginalization of patients. In rich countries, homeless, illegal immigrants, and active intravenous drug users, among others, will not benefit from the new HCV therapies in the short midterm. The high cost of new HCV drugs will represent a huge barrier for their wide use in resource-limited regions. Gradually, hepatitis C will become a disease of the poor.

In the long term, the complexity of current oral HCV antivirals will progressively vanish. More potent and simple drugs, including coformulations of several molecules (as in the HIV field), given as 1−2 pills once a day, with few drug−drug interactions and convenient safety profiles, will replace first-generation oral HCV antivirals, which still display limited potency, have to be given three times a day, cause drug interactions, and are often associated with serious adverse effects. Thus, although the immediate next couple of years of hepatitis C therapeutics will require significant medical expertise, we can envisage that beyond the next 5−10 years, therapies for hepatitis C will become much more simple. The current and shortly coming complex medication regimens, which are given with schedules resembling those used in oncology, will steadily be replaced by simple ones that perhaps would mimic those now used for treating *Helicobacter pylori*. As

result, hepatitis C care givers will shift again from super-specialists to general practitioners.

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Notes
The authors declare no competing financial interest.

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