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Commentary

The changing face of hepatitis C in the new era of direct-acting antivirals

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ABSTRACT

The approval of the first protease inhibitors as treatment for hepatitis C virus (HCV) infection is rapidly transforming the way patients with chronic hepatitis C are managed. Treatment regimens are moving to combinations given for shortened periods, excluding poorly tolerated subcutaneous interferon, and providing rates of cure exceeding 75%. The recognition of HCV infection as a systemic disease, not limited to producing liver damage, in which extrahepatic complications play a major role as the cause of morbidity and mortality, is prompting the treatment of a growing number of HCV-infected individuals. However, new challenges are emerging, including the need to diagnose a substantial proportion of asymptomatic carriers, the risk of potentially harmful drug–drug interactions and the high cost of medications. The future will probably see a progressive marginalization of residual HCV populations, with increasing over-representation of illegal immigrants, alcohol abusers, intravenous drug users and the mentally disabled.

1. Introduction

The US Food and Drug Administration approved boceprevir and telaprevir as treatments for chronic hepatitis C virus (HCV) infection in the spring of 2011. These two small molecules are competitive inhibitors of the NS3 viral protease. Their administration along with pegylated interferon-α plus ribavirin heralds a new era in the management of hepatitis C (Alter and Liang, 2012), somewhat resembling what happened in 1996 in the AIDS field, when the first HIV protease inhibitors were approved and triple antiretroviral combinations began to be widely used.

Triple combination therapy for hepatitis C, including either of the first two direct-acting antivirals (DAA), is currently recommended for patients infected with HCV genotype 1 (Ghany et al., 2011). In comparison with the previous regimen (dual therapy with peginterferon-α and ribavirin), overall response rates have increased from 35% to 70%, and in many subjects the length of therapy can be reduced from 12 to 6 months. The downside is that triple therapy significantly increases the patient's pill burden and side effects, and drug interactions and complicated treatment schedules require significant expertise by healthcare providers. Because the new drugs are quite expensive, curative therapy for hepatitis C cure is becoming something of a privilege for wealthy societies or individuals. However, the prospect of being able to cure most patients has prompted US public health authorities to recommend HCV testing for everyone born from 1945 to 1965 (DHHS, 2012).

2. Expanding hepatitis C treatment

The opportunity to cure most patients has increased interest in treating chronic hepatitis C beyond those with advanced liver disease. This situation resembles what has already occurred with HIV infection. For a long time, antiretroviral therapy was restricted to subjects with advanced immune deficiency. However, as the number of drugs increased, their potency enhanced and their safety improved, a larger number of HIV-infected individuals began treatment earlier. Most importantly, the benefit of antiretroviral treatment now extends beyond the correction of immune deficiency to reduce virus transmission and ameliorate the deleterious consequences of chronic inflammation caused by persistent immune activation. These effects accompany complete suppression of viral replication, even though HIV is not eradicated. For all these reasons, recent guidelines recommend treating almost everyone with HIV infection (Thompson et al., 2012).

For chronic hepatitis C, the major concern for most individuals is the development of end-stage liver disease, either decompensated cirrhosis or liver cancer, which life-long occurs in around 25% of patients. However, extrahepatic manifestations of HCV infection are common, and when possible should also prompt early treatment. These illnesses are caused by immune complexes (e.g., mixed cryoglobulinemia), or result from persistent inflammation

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and immune activation driven by continuous viral replication, resembling what happens in HIV infection. Although the appeal of preventing viral transmission is lower for HCV than for HIV, given the different efficiency of sexual transmission, the possibility of truly eradicating HCV is a unique claim (Table 1).

3. Extrahepatic manifestations of HCV infection

Table 2 summarizes the wide spectrum of dermatological, renal, neurological and cardiovascular manifestations associated with chronic HCV infection. The most common renal complication is type I membranoproliferative glomerulonephritis, usually in the context of type II mixed cryoglobulinemia. Several studies have shown that HCV infection is also associated with an increased risk of renal insufficiency or proteinuria (Peters et al., 2012).

Neurological complications ranging from peripheral neuropathy to cognitive impairment occur in a large number of HCV patients (Sarkar et al., 2012). The pathogenic mechanisms responsible for nervous system dysfunction in HCV infection are mainly related to up-regulation of host immune responses, with production of autoantibodies, immune complexes and cryoglobulins (Monaco et al., 2012). Accelerated atherosclerosis and cardiovascular disease also occur more frequently in patients with chronic hepatitis C, hypothetically as a result of the persistent activated inflammatory state (Maruyama et al., in press).

Recent findings from the REVEAL-HCV study have highlighted that extrahepatic complications contribute substantially to mortality in chronic hepatitis C patients (Lee et al., 2012). The authors followed 23,820 adults in Taiwan for an average of 16.2 years. HCV antibodies were reactive at baseline in 1095 patients, with serum HCV-RNA detectable in 69.4%. There were 2394 deaths during the study period. As shown in Fig. 1, both liver-related and extrahepatic complications contributed significantly to the nearly 2-fold increase in mortality seen in HCV-seroreactive individuals. Altogether, current knowledge suggests that therapeutic eradication of HCV will result in benefits beyond halting liver injury. Thus, if treatment becomes more efficacious and well tolerated, any infected person should be considered as candidate for therapy, following the roadmap already charted in the HIV/AIDS field (Thompson et al., 2012).

4. The growing public health burden of HCV infection

A more open consideration of the management of chronic hepatitis C has unveiled important gaps that must be filled if advances in therapeutics are to be translated into public health benefits. HCV has surpassed HIV in total annual deaths in the United States (15,000 versus 13,000), but more than half of chronically infected cases have not been diagnosed, largely due to the fact that patients with decompensated liver disease make up less than 10% of the HCV-infected population. In the United States, it is estimated that 2.7–3.9 million people, 1.3–1.9% of the general population, have chronic hepatitis C. The low rate of diagnosis is largely due to the lack of identifiable risk factors for infection in more than half of cases (those termed "*sporadic*") (Rein et al., 2012). This contrast with HIV, for which most infected persons acknowledge prior risk behaviors. As mentioned, a nationwide campaign for HCV diagnosis in "baby boomers" is currently under way in the US (DHHS, 2012).

The active search for HCV-infected persons through expanded screening should also include younger high-risk groups, such as intravenous drug users. The good news is that new infections have declined over the last two decades, following the introduction of antibody screening tests and harm-reduction campaigns among injecting drug users. Even so, some 18,000 new infections occur in the US each year (Ly et al., 2012). In comparison, there are 50,000 new HIV infections annually, and a total of 1.2 million infected people (0.5% of the population).

5. Advances in diagnostics

Advances in HCV therapeutics have coincided with the arrival of new technologies and diagnostic tools. Two major breakthroughs merit particular recognition. Liver biopsies are no longer required to assess the severity of hepatic damage, as noninvasive tools, including serum fibrosis indices and elastometry (*FibroScan*), now allow rapid, cheap and accurate assessment of the extent of liver fibrosis. In contrast to liver biopsies, these procedures can be performed repeatedly in the same patient. Given the high cost of DAA, the prioritization of treatment for subjects with significant or advanced liver fibrosis seems justified. However, delaying therapy to cirrhotic stages is penalized by a reduced likelihood of viral clearance and more frequent and severe toxicities. As therapies for hepatitis C become simpler and hopefully cheaper, most if not all patients will be considered to be candidates for treatment, regardless of their liver fibrosis stage and/or co-morbidities (Barreiro et al., 2012).

Another landmark discovery is that a genetic polymorphism in IL28B strongly influences the response to HCV therapy, highlighting the role of innate immunity in the clearance of the virus (Ge et al., 2009; Rallón et al., 2010). This finding suggests that personalized medicine, with genotypic screening preceding drug treatment, will become more common in the near future. Individualization of therapy will include a once-in-a-lifetime baseline assessment, using microarrays, to test for several gene polymorphisms. Treatment decisions will then be based on genetic profiles, including IL28B, ITPA, ENT-2, UGT 1A1, CYP 3A4, LDLr and perhaps HLA DQ*0301 (Soriano, 2012; Soriano et al., 2012).

6. Interferon-free, oral DAA combinations

The current armamentarium against HCV will soon be expanded with molecules belonging to different drug families, including new NS3 protease inhibitors, NS5B polymerase inhibitors (nucleoside and nucleotide analogues and others), and NS5A inhibitors. More than ten drugs are currently completing phase II–III trials, in regimens with or without interferon and/or ribavirin (Table 3) (Lange and Zeuzem, in press; Soriano et al., 2012).

Oral regimens without subcutaneous peginterferon-α are no doubt the most promising, once proof-of-concept testing has

Table 1
Expected effects of antiviral therapy on HIV and HCV infections. ARV: antiretroviral therapy. DAA: direct-acting antivirals.

	ARV (HIV)	DAA (HCV)
Viral replication	Suppression without clearance	Eradication
Major clinical benefit	Reversal of immune deficiency	Reversion of liver fibrosis
Drug-related toxicity	Long lasting, cumulative	Short-term, reversible
Chronic inflammation and persistent immune activation (premature aging)	Amelioration	Elimination
Transmission	Reduction	Elimination