Evolution and Revolution of Hepatitis C Management: From Non-A, Non-B Hepatitis Toward Global Elimination

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Keywords

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Abstract

Discovery of hepatitis C in 1989 allowed basic research to identify critical components of hepatitis C virus (HCV) structure and life cycle. Interferon (IFN)-α was introduced as first treatment for chronic hepatitis C and later was enhanced by pegylation, addition of ribavirin, and resulted in improved sustained virologic response. Better understanding of HCV structure, enzymes, and lifecycle led to the discovery of direct-acting antivirals and IFN-free era. Successful HCV therapy created a rare possibility of global disease eradication, which is now a major goal internationally. However, hepatitis C remains a major public health challenge, and more resources are needed to reach global elimination.

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Introduction

This review article summarizes a fascinating history of hepatitis C virus (HCV). Here in this paper, we cover historical aspects of HCV discovery, early treatment options, and breakthroughs brought by direct-acting antiviral

(DAA) drugs. The review is also aimed to discuss remaining challenges and future steps needed for global HCV elimination in the next decades.

Non-A, Non-B Hepatitis, and Discovery of Hepatitis C

In the 1960s, viral hepatitis was first classified as classical infectious hepatitis, characterized by short incubation period, short period of abnormal serum transaminase activity, and high degree of contagiousness or as serum hepatitis that had longer incubation and abnormal serum transaminase activity periods, was moderately contagious, and could result in chronic hepatitis [1]. In 1965, Blumberg et al. [2] discovered Australia antigen, later named the hepatitis B surface antigen (HBsAg), that was linked to viral hepatitis and at that time considered to be the main cause of serum hepatitis [3, 4]. In order to prevent post-transfusion hepatitis, sensitive tests for HBsAg were developed [5]. Donor screening for HBsAg reduced post-transfusion hepatitis cases by 50%; however, there still were some hepatitis cases, despite the fact that patients received only blood that was HBsAg negative [6]. In 1975, Feinstone et al. [7] detected hepatitis A virus in stool of infected patients and when serological test to detect both hepatitis A virus and HBV were developed, it was found

that parenterally transmitted hepatitis is caused by another virus, named “non-A, non-B” hepatitis (NANBH) [8]. Chimpanzee studies showed that multiple NANBH agents are present, and one of them is small enveloped agent that causes membranous tubules within the cytoplasm of hepatocytes [9–11]. Simultaneously, progression to liver cirrhosis [12], as well as to hepatocellular carcinoma [13], was confirmed in NANBH patients. Hoofnagle et al. [14] started a pilot study where NANBH was treated with interferon (IFN)- α 2b. Those were the same regimens that showed to be effective in treating patients infected with hepatitis B. Results revealed that on IFN therapy serum aminotransferase levels decreased rapidly [14]. Despite these findings, over a decade of intensive laboratory research was needed to finally discover the disease-causing agent. In 1989, the NANBH virus genome was cloned and sequenced by Houghton et al. [16] and called HCV [15]. This discovery allowed sensitive tests to detect HCV and eliminate the virus from the blood transfusion supply.

Cracking the Structure of Hepatitis C

After successful identification of HCV, following genetic analyses revealed complete sequence of the HCV genome which consists of a positive-stranded RNA molecule of approximately 9,600 nucleotides [17, 18]. The genome consists of an open reading frame encoding a polyprotein precursor of 3,010 amino acids [19]. Translation and replication of the HCV open reading frame are directed via a 340 nucleotide long 5' untranslated region. The HCV polyprotein is cleaved by host and viral proteases into 10 different products, with the structural proteins (core, E1 and E2) and the nonstructural (NS2–5) replicative proteins [19]. HCV is an enveloped virus [20] that replicates in hepatocytes [21]. While envelope glycoproteins E1 and E2 help virus to enter the hepatocyte [21], liver-specific microRNA-122 contributes to stability, translation, and replication of the HCV RNA [22, 23]. HCV is a member of *Flaviviridae* family and belongs to *Hepacivirus* [20]. It also has a similar genome organization as *Pestivirus* (bovine viral diarrhea, classical swine fever), *Flavivirus* (yellow fever, zikavirus, dengue virus), and *Pegivirus* (human virus GBV-C) [20, 24]. In 1993, phylogenetic analyses revealed high genetic heterogeneity of the virus and classified HCV into 6 genotypes (GTs) [25–27]. Subtypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a are currently the ones which are studied in detail [28]. In 2014, Smith et al. [29] reported GT7, more recently GT8 was confirmed in 4 patients from India [30]. A global survey

found that HCV GT1 and 3 are the most prevalent GTs and account for 46 and 30% of all HCV cases, respectively; GTs2, 4, 5, and 6 accounted for the majority of remaining cases: 9, 8, 1, and 6%, respectively [31]. Today, exact determination of GT and subtype provide us not only with information about geographical prevalence in different countries but also is important for targeted anti-HCV treatment.

Historical Treatment Options for Hepatitis C

After first attempts to treat HCV patients with IFN- α 2b [14], 2 randomized controlled trials were started. One study administered 2 million units of IFN- α 2b versus placebo 3 times weekly [32], another study used either 3 or 1 million units versus placebo 3 times weekly [33]. In both studies, the course of treatment lasted for 6 months. The results showed that IFN- α 2b was efficient in reducing disease activity; however, after the cessation of treatment, many patients relapsed [32, 33]. To assess the effect of IFN- α 2b therapy, HCV RNA levels were detected in another study, which confirmed that HCV RNA was successfully decreased or eradicated in some patients after IFN- α 2b therapy [34]. After these studies, IFN- α 2b was officially approved for chronic hepatitis C treatment; however, frequent side effects, high relapse rate, and average sustained viral response (SVR) [35] suggested that another agent was needed. The first attempts to treat chronic hepatitis C with ribavirin monotherapy were initiated in early 1990s. The results were immediate: ALT levels decreased rapidly, but after discontinuation of the treatment, almost in all patients, ALT levels rose back to pre-treatment levels [36, 37]. These findings led to the initiation of clinical trials, where INF- α was combined with ribavirin in patients with chronic hepatitis C [38, 39]. In both studies, patients were randomized to receive INF- α alone or along with ribavirin, and results showed that combined therapy was significantly associated with higher SVR or even complete HCV RNR clearance. After large-scale multicenter randomized trials confirmed these findings [35, 40], the combination of INF- α and ribavirin was approved as a standard treatment of chronic hepatitis C in 1999. INF- α 2b and ribavirin were administered 3 times per week, and for many patients, this regimen was difficult and related to the rapid clearance of the drug [41]. To maintain a steady level of an active drug and reduce the frequency of administration, pegylated INF- α 2b (PegINF- α 2b) was developed. Following studies showed that PegINF- α 2b was superior to the unpegylated

Fig. 1. Timeline of milestones in hepatitis C discovery and treatment. HCV, hepatitis C virus; NANBH, non-A non-B hepatitis; IFN, interferon, PegINF, pegylated interferon; SOF, sofosbuvir, LDV, ledipasvir; DAA, direct-acting antiviral; NS, nonstructural.

IFN [41], and new combination of PegINF- α 2b and ribavirin became the standard choice of hepatitis C treatment for the next 10 years. During these years, treatment response and duration were determined by measuring HCV RNA levels at baseline, weeks 4, 12, and 24, at the end of treatment, and 24 weeks after treatment [42]. Genome-wide association studies also contributed by identifying single nucleotide polymorphism located in interleukin-28B (*rs12979860*), which is strongly associated with positive INF- α treatment response and spontaneous HCV clearance [43]. However, better understanding of HCV structure, enzymes, and lifecycle led to the introduction of new drug targets and the discovery of DAAs.

DAA Drugs

In 2011, first DAAs (telaprevir and boceprevir), used in combination with PegINF- α and ribavirin, were officially approved for HCV GT1 treatment [42]. Both drugs are NS3-4A protease inhibitors and their effect results in inhibition of HCV replication. Despite the fact that clinical trials results were promising, adverse events and serious complications showed that there is a need for improvement [44–46]. After a few years of intensive research, safer and more effective DAAs were developed

(Figure 1). In 2013, simeprevir was approved in combination with PegINF- α and ribavirin for HCV GT1 and showed less side effects with same SVR rates [47]. The same year sofosbuvir, an NS5B polymerase inhibitor, was developed and showed to be effective against all HCV GTs [48, 49]. It was approved as a part of therapy for HCV GT1 and GT4 with PegINF- α and for GT2 and GT3 with ribavirin. After 3 clinical trials found that DAAs can be used alone for HCV GT1 treatment with SVR rates of 94–99% and with significantly less side effects, in 2014, FDA approved first all-DAAs regimen with sofosbuvir/ledipasvir and sofosbuvir/simeprevir [50–53]. To date there are many available EMEA- and FDA-approved DAAs for HCV treatment, which are classified according to their chemical structure: protease NS3 inhibitors (glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir), NS5A serine protease inhibitors (daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir), NS5B RNA-dependent RNA nucleoside polymerase (sofosbuvir), and non-nucleoside polymerase (dasabuvir) inhibitors [54]. These drugs differ in their action mechanism against the different HCV GTs and their combinations enable higher barrier to resistance [55]. Because of their virological efficacy, ease of use, safety, and tolerability DAA-based regimens are being used in HCV-infected patients without cirrhosis and with compensated cirrho-

Fig. 2. Hepatitis C elimination challenges. HCV, hepatitis C virus.

sis, “treatment-naïve” patients, and in patients who were previously treated with IFN and ribavirin [56]. The success in HCV therapy created a rare possibility of local disease elimination or even global disease eradication. To achieve this, more effective, well tolerated, and highly available therapy is still needed in the future.

Heading Toward Global Elimination of Hepatitis C in 2030

Hepatitis B and C infections remain one of the dominant causes of liver-related deaths [57]. Globally, in 2015, 257 million people were living with chronic HBV infection, 71 million people with chronic HCV infection, and 1.75 million new HCV infections occurred worldwide [58]. Major public health activities are needed to combat viral hepatitis and reduce burden of these chronic diseases. In 2016, the World Health Assembly adopted the Global Health Sector Strategy to eliminate viral hepatitis by 2030 [58–60]. The WHO goal for HCV infection is to decrease number of incidence by approximately 90% and reduce number of HCV-related deaths by approximately 65% in 2030 [60]. Key public health interventions for both HBV and HCV were determined: HBV vaccination, prevention of mother to child transmission of HBV, injection and blood safety, harm reduction, test and treatment of HBV

and HCV [60]. To successfully cut down the incidence of hepatitis C, it is needed to improve education on injection safety and vein care, appropriately screen blood transfusions, reduce the use of unnecessary injections, and provide sterile syringes and medication-assisted treatment to people who inject drugs [60, 61]. Elimination of HCV-related deaths depends on efficacious test and treatment strategy. While HCV-specific antibodies can be detected up to 99% sensitivity and specificity, there are many difficulties in diagnosing HCV infection, mainly because HCV infections are asymptomatic [60]. Also, reaching high-risk groups, such as people who inject drugs and prison inmates, is always difficult and requires specific public health interventions. The remaining elimination challenges are lack of political prioritization, insufficient funding for HCV treatment and screening, treatment restrictions applied by physicians (e.g., for patients with psychological disorders, substance abuse), insufficient number of treaters, no systematic screening, and diagnosis programs and suboptimal linkage to care [60–62] (Figure 2). Lack of financial resources also remains the major obstacle to eliminate hepatitis by 2030. Worldwide, the commitment to develop national plans is improving. As of March 2017, 43 WHO Member States have reported that they have developed national plans, and 36 have reported that plans are in progress; however, only a few countries included hepatitis treatment and prevention strategies for all patients in their national hepatitis programs [57, 62]. According to Polaris data, Australia, Iceland, Switzerland, Italy, Mongolia, Spain, Egypt, France, Georgia, Japan, Netherlands, and United Kingdom are on their way to achieve the WHO hepatitis elimination targets [63, 64]. In low-income countries, current hepatitis B and C treatment rates are very low and strong financial and political will, support from civil societies, and support from pharmaceutical and medical companies is needed [65, 66].

Conclusion

The remarkable history of the discovery of HCV and an exciting era in HCV treatment could lead to an exceptional possibility of global elimination of the virus. However, drug price reduction and international collaboration are compulsory to obtain this goal.

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V.B.-B. and J.K.: contributed in data analysis and writing original manuscript. J.K. contributed in reviewing and editing manuscript. V.B.-B. contributed in visualization of manuscript. All authors reviewed and approved of the final manuscript.

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