

Next Steps Toward Eradication of Hepatitis C in the Era of Direct Acting Antivirals

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Abstract

Context: After the introduction of safe and highly effective hepatitis C virus (HCV) treatments, eradication of HCV in the next 20 years is the ultimate goal. Since 2011, the advent of first generation direct acting antivirals (DAAs) were started and followed by the introduction of a new wave of DAAs in 2013 which exhibit outstanding efficacy. It is obvious that the eradication of hepatitis C is not restricted to development of DAAs.

Evidence Acquisition: An electronic search of available literature published was conducted in all peer-reviewed journal indexed in PubMed, Scopus and Google scholar. The literature search was done among articles related treatment of hepatitis C with DAAs in different patient groups with mass screening of the patients and cost benefit of new treatments as main key words.

Results: There are major steps that should be taken to eradicate HCV, including (1) the development of screening strategies, particularly for groups such as intravenous drug users and recipients of blood or blood products before the introduction of HCV screening in donors; (2) the development of strategies to overcome issues with the high cost of recently introduced treatments; (3) special attention to special patient groups, such as HIV/HCV co-infection, hemophilia, thalassemia, hemodialysis, and liver-transplant patients; and (4) development of preventive strategies, such as the development of an efficient HCV vaccine, special attention to harm reduction in high-risk groups, and promotion of mass awareness of HCV.

Conclusions: The eradication of HCV will require significant governmental financial investment for screening, prevention, and treatment of infected patients. Although, we have a long way to eradication of HCV, the next steps could be including proper planning to patient finding, availability of new treatments to all patients and development of HCV prevention strategies such as vaccines.

Keywords: Hepatitis C, Diagnosis, Mass Screening, Treatment Outcome

1. Context

It is estimated that chronic hepatitis C (CHC) affects more than 180 million people worldwide, which is about 3% of the world population (1). An increase in hepatitis C virus (HCV)-related morbidities and mortalities has been observed in recent years. In addition, increasing rates of advanced liver disease as a result of HCV infection are expected to be observed in the next decade, and developing countries, which have a higher prevalence of HCV infection, will experience the major burden of end-stage liver diseases (ESLD) throughout the world (2-4). Therefore, it is obvious that this infection is a major concern of health policy makers. Fortunately, the risk of developing hepatocellular carcinoma (HCC) as one of the main complications of HCV infection can be reduced by 75% with successful treatment (5), and today, newly introduced treatment strategies have provided opportunities to manage and control this

public health concern (6, 7).

2. Evidence Acquisition

In the present study, we conducted an electronic search of available literature published to find pertinent contents reporting novel HCV treatments toward clearance in all HCV infected patient groups and cost benefits of new treatments in the era of DAAs. To identify articles, the search was begun among all peer-reviewed journal indexed in PubMed, Scopus and Google scholar. The literature search was done by using the following key words: "Hepatitis C virus, HCV, HCV genotypes, special groups, HIV/HCV co-infections, thalassemia, hemophilia, hemodialysis, liver transplantation, mass screening, diagnosis and treatment outcome". The search results were investigated carefully, and then most relevant results were strongly considered

for including in this study by all authors and consulting the supervisor of the study (SMA).

3. Results

3.1. The Evolution of Hepatitis C Treatment

Treatment of HCV infection has a long history. It began with interferon (IFN) mono-therapy, with less than 20% sustained virological response (SVR). Milestones include the addition of ribavirin (RBV) to the treatment protocol and providing pegylated-IFN (PegIFN) as an alternative treatment (8-10). Treatment with PegIFN/RBV was the standard of care for about 10 years, and it allowed about 50% of subjects with HCV genotype 1 infection to attain SVR (10-12). The success rate of treatment with this regimen is very dependent on patient characteristics, including age, body mass index, ethnicity, and genetic factors such as polymorphisms near the Interferon Lambda 3 (*IFNL3*) gene (13, 14). Viral factors, especially HCV genotype, also affect the response to HCV treatment (15), and there are always additional factors that should be taken into account in each treatment approach, including treatment success rate, duration, cost, and side effects. In light of these concerns, attempts have continued to introduce better therapeutic regimens (10, 16). Treatment of chronic HCV infection has been revolutionized in recent years. Knowledge of the HCV replication cycle and the role of viral proteins in the virulence of HCV have resulted in targeting of the viral proteins involved in the HCV life cycle to develop new HCV treatments. In 2011, the first generation of direct acting antivirals (DAAs) Boceprevir (BOC) and Telaprevir (TVR) were introduced and added to the previous PegIFN/RBV regimen (17, 18). These new triple therapy strategies led to higher SVR, but they were still IFN-based and had severe adverse effects. Triple therapy with BOC or TVR quickly fell out of favor due to the introduction of a new wave of more efficient DAAs beginning in 2013, which changed the standards for HCV treatment. In December 2013, the FDA approved Sofosbuvir (SOF) in combination with PegIFN/RBV for treatment of HCV genotype 1 infection. This approach achieved a response rate of over 85%; however, the presence of unfavorable treatment predictors such as cirrhosis, previous history of treatment, and unfavorable host genetics can influence the success rate of treatment with SOF/PegIFN/RBV (19). SOF in combination with RBV and/or PegIFN was also approved for treatment of HCV genotypes 2, 3, and 4, with limited efficacy for HCV genotype 3 (20). In October 2014, the FDA approved Ledipasvir (LDV) in combination with SOF for treatment of HCV genotype 1, which achieved more than 95% efficacy (21, 22). Fortunately, in addition to being more effective than the previous SOF/PegIFN/RBV reg-

imen, SOF/LDV is influenced little by patient characteristics. In December 2014, the FDA approved another IFN-free DAA regimen a combination of Ombitasvir/Paritaprevir/Dasabuvir (a three direct acting antiviral, or 3D) for treatment of HCV genotype 1 infection, with an efficacy rate of over 95% (23). Finally, in January 2016, the FDA approved combination therapy with Grazoprevir/Elbasvir (GZR/EBR), with about a 95% SVR rate (24). Other regimens containing DAAs, such as Simeprevir (SMV) and Daclatasvir (DCV), have also been approved for treatment of HCV infection since 2013 (25, 26).

3.2. Next Steps for Eradication of HCV Infection

The use of new treatment strategies has provided opportunities to eradicate HCV infection. However, effective treatment is not enough; there are still major issues that must be taken into account, some of which we address in this paper.

3.3. The Necessity of Mass Screening

Although an effective treatment regimen is a necessary tool in infection eradication, identifying infected individuals is also of vital importance. Subjects with HCV infection can remain asymptomatic for a long time, so they may be unaware of their infection. During this period, infection can progress to advanced liver disease, and the patient may spread the virus to others. Surprisingly, about 75% of patients with HCV in the United States are unaware of being infected (27). Another challenge to developing screening strategies for HCV is the occult nature of this infection, which cannot be identified with routine diagnostic tests (28, 29).

We believe that health policy makers should design powerful screening programs to identify HCV-infected subjects. Risk factors for HCV infection include intravenous drug use (IVDU), history of unsafe injection practices, use of blood and/or blood products before the introduction of blood donor screening for HCV between 1992 and 1996 (depending on the national policies of different countries), being homeless, and history of imprisonment (30). The prevalence of these risk factors varies among different populations and countries; population-based studies have determined that different geographical regions have unique risk factors for HCV infection. For example, baby boomers, persons born between 1945 and 1965 in the United States, account for about 70% of HCV infections in the US (31). In addition, previous parenteral therapy for schistosomiasis is a significant predictor of HCV infection in Egypt (32). However, in some countries, further population-based studies are required to determine the special risk factors related to each area. Once this is done,

subjects with these risk factors can be recognized as special groups and singled out for screening. These population-based studies should be conducted alongside the implementation of new prevention and treatment strategies in order to track changes in geographically-based risk factors and changes in the prevalence of HCV among subjects with these risk factors. These studies will also help in the evaluation of screening strategies.

As a result of geographical differences in risk factors and prevalence, a different screening strategy is needed for each country, and this should be supported by governmental and non-governmental organizations. Governments should pay attention to this important issue and fund screening, and health policy makers should design a risk-based, powerful screening method. Furthermore, the quality of these activities and screening methods should be evaluated by research projects and epidemiological population-based studies, which can guide policy makers. Ultimately, medical practitioners and healthcare personnel have an important role in this regard, and they must support screening projects.

Risk-based screening strategies can identify about 86% of patients with HCV (33). This is good, but is it sufficient for HCV eradication? Some patients do not have traditional risk factors and therefore cannot be identified by risk-based screening. Therefore, worldwide clinical screening, together with the approach of risk-based screening (34), is recommended. However, the feasibility of such an approach is highly dependent on the economic situation of a given country.

3.4. Cost/Benefits of New Treatment Strategies

One of the main inconveniences of new treatment strategies is their current high cost. For example, the cost of a 12-week treatment with SOF is 85,000 - 110,000 USD. New treatment approaches have shorter durations, minimal adverse effects, and higher efficacy; however, they are very expensive. Strategies should be applied to reduce treatment costs and provide wide access to new treatments, especially in low- and middle-income countries, in which about 80% of patients with CHC live (5, 35, 36).

3.5. Special Patient Groups Need Special Attention

Special patient populations include every group that represents a unique challenge to HCV treatment. People with inherited bleeding disorders (such as hemophilia), people with inherited hemoglobin disorders (such as thalassemia), patients under hemodialysis, patients with organ transplantation (especially liver- and kidney-transplant patients) and HCV patients co-infected with HIV are some of the groups that need special attention

and priority in treatment (37). Special patient groups with CHC are at increased risk of death or complications (38). A basic question arises here: What considerations need to be made for special patient groups in the era of DAAs? These populations are the most challenging to treat, and they require massive attention. Because of faster progression to both ESLD and HCC in special patients, HCV is a significant cause of morbidity and mortality in these populations (39).

HIV/HCV Co-infection: HIV and HCV co-infection poses a challenge because it is widespread, particularly among IVDUs, and it exhibits lower rates of spontaneous HCV clearance, poor response to treatment of chronic HCV in the pre-DAA era, and more rapid progression of HCV-related liver diseases such as cirrhosis and HCC (40). Global statistics indicate that four to five million people are co-infected with HIV/HCV (41). Adoption of interferon-based HCV treatments (following the PegIFN/RBV and first-generation HCV protease inhibitors) resulted in lower SVR in those with HIV/HCV co-infection than in those with HCV mono-infection (40). Furthermore, HCV treatment regimens involve serious adverse effects and pharmacokinetic drug interactions with HIV-antiretroviral drugs (42-44). The development and approval of new oral regimens of DAAs has created an opportunity to improve HCV treatment efficacy and safety for HIV/HCV co-infected patients. However, drug interactions between HCV DAAs and HIV-antiretroviral agents are still a major problem. For example, SMV and 3D regimens are contra-indicated in HIV patients receiving many protease inhibitors. Today, SOF plays a key role in treating HIV/HCV co-infection; it has a lower degree of interaction with HIV-antiretroviral drugs. The combination of SOF/LDV or SOF/DCV provides high rates of SVR in HIV/HCV co-infected patients. Recently, the use of SOF/LDV and SOF/DCV has been shown to be effective and safe in patients with HIV/HCV co-infection, achieving SVR rates of 98% and 96% - 98%, respectively (45, 46). Although there has been much progress in the field of HIV/HCV co-infection treatment, this patient population still needs more attention.

Thalassemia and Hemophilia: HCV infection is one of the most common infections following the use of blood and blood products among thalassemia and hemophilia patients (47). The treatment of thalassemia patients infected with HCV is a very controversial issue. Dual therapy with PegIFN/RBV, use of protease inhibitors (BOC and TVR), and PegIFN/RBV-based triple therapy leads to RBV-associated life-threatening anemia in many thalassemia patients (48). On the other hand, the elimination of RBV and the use of low-dose RBV in the treatment of thalassemia patients seems to result in low SVR rates (49). Nevertheless, because of the severe adverse effects of RBV-

based treatments in these patients, it is very important to utilize RBV-free regimens. Unfortunately, there are currently no clinical trials evaluating the effect of DAA use to treat HCV infection in thalassemia patients. Although the combination of PegIFN and RBV is still used in treatment of HCV-infected thalassemia patients (15), a few thalassemia cases have been treated with SOF-based treatment in our clinic (Middle East liver disease center) and experienced a favorable treatment response. However, clinical trials with new DAAs are required to evaluate this approach.

Individuals with hemophilia have been disproportionately and unexpectedly affected by HCV (50). Liver failure due to HCV infection is one of the common causes of death in patients with hemophilia. Anti-HCV therapy plays a vital role in the interruption of the HCV infection pathway in order to prevent cirrhosis and HCC. The current standard of care for treatment of HCV in hemophilia is PegIFN/RBV, which achieves SVR in 61% of patients (51). However, the side effects of the PegIFN/RBV regimen, including thrombocytopenia and excessive bleeding, should be considered. A recent open-label study showed that out of 14 hemophilia patients infected with HCV and treated with SOF/LDV, all achieved SVR (100%) (52). Despite the increasing use of highly effective anti-HCV agents with minimal side effects to treat hemophilia patients, hemophiliacs still constitute a unique patient population that requires special consideration.

Hemodialysis: HCV infection is one of the most common infections transmitted by the parenteral route in patients receiving maintenance hemodialysis (53). The use of RBV is problematic in this group. Receiving an IFN-free and, if possible, RBV-free regimen is a fundamental, urgent need in patients under hemodialysis (51). In persons with renal impairment receiving chronic hemodialysis, options for HCV treatment are limited. DAAs are contra-indicated for patients undergoing dialysis. However, Asunaprevir, DCV, SMV, GZR/EBR, and 3D regimens are cleared by hepatic metabolism and can be used in patients with renal disease (54).

Liver Transplantation: Hepatitis C recurrence is common after liver transplantation when patients are transplanted with detectable viral loads. Recurrence of HCV following liver transplantation may accelerate graft injury, which is difficult to treat with IFN/RBV therapy (55). Antiviral treatment before transplantation can prevent HCV recurrence. IFN-based regimens are poorly tolerated and are either ineffectual or contra-indicated in most liver-transplant patients (56). In contrast, SOF-based regimens have satisfactory virological response in more than 80% of post-transplant patients (57).

Favorable response to the currently available therapies and new highly effective treatments for HCV revealed that

HCV clearance could be significantly improved in special patient groups. DAA-based therapies stand to achieve a very high rate of treatment success with minimal side effects.

3.6. Prevention Strategies

The introduction of new therapeutic agents does not detract from the importance of preventive strategies, including the development of an HCV vaccine (58). It seems that an effective vaccine is achievable in the near future, and as Bill Gates has said, "Treatment without prevention is simply unsustainable." Studies on vaccine development should be prioritized. On the other hand, reduction of harmful behaviors should be the main strategy to reduce the prevalence of HCV infection in certain high-risk groups, such as IVDUs and inmates (27, 30). Furthermore, public knowledge and awareness are vital to the eradication of every disease, and ignorance will prevent future eradication of HCV.

4. Conclusions

Treatment of HCV infection has been revolutionized in recent years. New treatments have a higher rate of success, less severe side effects, and a shorter duration of therapy. The main goal for the hepatology and infectious disease communities is the eradication of HCV in the next 20 years; however, HCV eradication will be an uphill battle. The next steps are (1) finding and treating patients with HCV infection in the general population; (2) improving the availability and affordability of effective treatments in developing countries, which will bear the majority of the burden of liver diseases in the next decade without proper management; (3) combatting HCV infection in special groups, such as patients with thalassemia, HIV/HCV co-infection, kidney disease, and liver-transplant patients; and (4) concentration on prevention alongside treatment, always remembering that prevention is better than a cure.

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