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Approaches and Considerations for the Successful Treatment of HCV Infection

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Abstract

The complexity of the hepatitis C virus (HCV) infection is reflected in its therapy, and great efforts are needed from the patient and the physician to be successful in eliminating the infection. How HCV will progress depends a lot on patient characteristics and social factors, in addition to the timing of initiation, duration, and final results of the therapy. The first treatment approved for patients with chronic hepatitis C was interferon (IFN) which had a sustained viral response (SVR) rate in 20%. Due to side effects, the adherence to this treatment was limited and required a patient-tailored approach with various medical disciplines working together and intervening at the right time to minimize potential obstacles. The introduction of direct-acting antivirals (DAAs) has contributed to the advancement of HCV treatment. However, a major obstacle to wide use of DAAs is their high price which has largely limited access to treatment. Guidelines and recommendations on treatment of hepatitis C have been developed to assist physicians and other health care providers to determine priority. Despite that, the arrival of new oral therapies has been met with enthusiasm as shorter, simpler, safer treatment allows for the possibility of delivering antiviral therapy on a large scale.

Keywords: HCV treatment, patient-tailored approach, treatment development, treatment goals, treatment priority

1. Introduction

Nowadays, the complexity of HCV infection is reflected in its therapy, and great efforts are needed from the patient and the treating physician. As a chronic disease with potential progression to fibrosis and HCV-associated cirrhosis, therapy of HCV in patients with liver disease and

post-liver transplant patients represents a challenge for physicians. Initiation, duration, and final results of the therapy depend on various factors such as viral factors, patient characteristics, and numerous social factors. The patient-tailored approach and close patient-physician cooperation as well as the role of various medical disciplines working together and intervening at the right time is important to decrease the potential barrier in the achieving an SVR.

2. HCV infection: complexity of infection

HCV is a single-stranded positive-sense RNA virus which belongs to the genus *Hepacivirus* of the Flaviviridae family. The most significant nonstructural (NS) proteins involved in virus replication include the NS3 helicase, NS3-NS4A serine protease, and the NS5B RNA-dependent RNA polymerase [1]. There are six known genotypes and a single known case of genotype 7 and more than 50 subtypes. Because the highest prevalence of genotype 1 is found in the most of middle-income countries, many DAAs have been primarily developed for use in those countries. Some DAAs are effective against multiple HCV genotypes. They are less effective for genotype 3 and cirrhosis [2].

The most significant clinical problems of chronic hepatitis C (CHC) involve the development of liver cirrhosis, hepatocellular carcinoma (HCC), or the need for liver transplantation [3, 4]. Progression of liver disease is more likely in patients with older age, male sex, longer duration of infection, advanced histologic stage and grade, genotype 1, increased hepatic iron, concomitant liver disorders, HIV infection, and obesity [5]. As many as 74% of people suffer from extrahepatic manifestations, and fatigue is the most common symptom. There are immune complex-mediated extrahepatic complications, glomerulonephritis, lymphoproliferative disorders such as B-cell lymphoma and extrahepatic complications unrelated to immune-complex injury (Sjögren's syndrome, lichen planus, porphyria cutanea tarda, type-II diabetes mellitus, and the metabolic syndrome) [2].

Recurrence of HCV following liver transplant occurs in more than 95% of patients and reinfection occurs within 72 h [2]. Not all patients can receive therapy instantly on the approval of new agents, so priority should be given to those patients with the most urgent necessity [6]. About 80% of patients treated with interferon-based treatment experience adverse effects. Hence, the close monitoring, timely preventive, therapeutic measures, and patient motivation are needed. Furthermore, adverse effects vary between drugs and range from poor general well-being to specific conditions affecting hematopoiesis, skin, behavior, thyroid, eyes, or lungs, and therefore, a multidisciplinary approach is necessary [7].

3. HCV treatment options goals and timeline development

CHC caused by infection with HCV is one of the major causes of liver disease. The goal of hepatitis C treatment is to achieve SVR defined as no detectable HCV in blood at least 12 weeks after finishing treatment. If a durable SVR can be achieved, the risks for liver-related morbidity and mortality are decreased [2].

In infected patients, IFN-mediated immune response is associated with the induction of IFN-stimulated genes (ISGs) in the liver [9] during the first 4–10 weeks of infection. This is followed by an HCV-specific T cell response [8]. However, the virus persists in 80% of infected patients. To boost the immune response, in 1989, interferon-alfa (IFN- α) was first developed, and in the decades that followed IFN- α , monotherapy was the standard therapy for hepatitis C. While developing the best regimen, various doses and durations of treatment were tested, but SVR rates remained modest (15–20%) [8].

The natural history of the HCV does not differ significantly among genotypes. However, HCV genotype 3 induces liver steatosis more often than the other genotypes. Patients with different genotypes can differ in their response to treatment with recombinant IFN- α and DAAs. Treatment efficacy has shown progressive improvement following the pegylation of IFN- α and its effect in combination with other antiviral drugs. However, viral escape mechanisms, IFN- α signaling in the liver, and substantial drug toxicity still restricted the efficacy of this treatment [9]. The restricted efficacy of IFN- α treatments stimulated considerable research efforts of academia and industry with the aim of understanding the mechanisms of nonresponse to IFN- α [10]. Recently, numerous studies showed association between genetic variants near the IFNL3 known as IL28B gene and the response to IFN- α treatments [11]. The molecular mechanisms that link genetic variation in the IFNL3 gene locus to the response to IFN- α remains to be investigated [12].

Combining IFN- α with ribavirin (RBV) became the new standard therapy in 1998. RBV had been used as a monotherapy for CHC in the 1990s, and it was discovered to transiently decrease serum alanine aminotransferase (ALT) levels during therapy [13, 14]. Subcutaneously injected interferon- α 2b (INF- α 2b) with daily oral RBV achieved an SVR in 38%. SVR was 54–56% after pegylated INF α (PEG-INF) was introduced. Until 2011, when the interferon-free era began, hepatitis C was treated with 6–12 months of weekly PEG-INF injections and twice-daily RBV tablets [2, 8]. Oral DAAs have simplified treatment procurement and delivery and improved HCV treatment outcomes. Numerous trials of interferon-free, oral DAA regimens have reported cure rate of more than 85% regardless of HCV genotype, many in only 12 weeks [5]. To date, it is assumed that high serum concentrations of IFN- α which are obtained after therapy with PEG-INF ensure a crucial advantage compared with nonpegylated forms of recombinant IFN- α [9].

In 2014, four classes of DAAs were described: NS3/4A protease inhibitors, non-nucleoside polymerase inhibitors, nucleoside/tide polymerase inhibitors, and NS5A inhibitors [5]. In general, DAA regimens are better tolerated and more effective than PEG-INF and RBV. Boceprevir and telaprevir—two HCV protease inhibitors—were developed to be given in combination with RBV and PEG-INF. This combination prevented emergence of HCV mutants with genetic resistance to the protease inhibitors. For the first time, an SVR could be achieved in more than 75% of individuals that were infected with the HCV genotype 1 [15, 16]. HCV non-nucleoside polymerase inhibitors (dasabuvir) are twice-daily drugs developed primarily for genotype1 [17, 18]. HCV nucleoside/tide polymerase inhibitors, such as sofosbuvir, are taken once daily and generally have a pangenotypic activity, potency, high resistance barrier, and low propensity for drug-drug interactions. HCV NS5A inhibitors

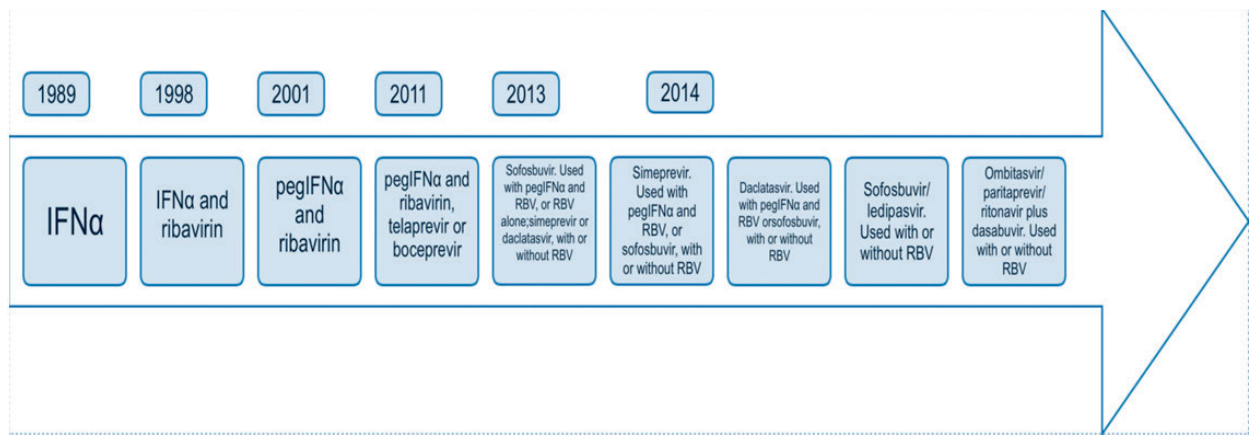


Figure 1. HCV Therapeutic Timeline.

(daclatasvir, ledipasvir, and ombitasvir) are novel drug class that are potent and have low barrier to resistance (**Figure 1**). So further research is needed to prevent or overcome drug resistance. On the other hand, daclatasvir and ledipasvir are pangenotypic and are well suited for combination with other DAAs [16].

4. Approach considerations in the IFN treatment era

Adherence to therapy is one of the most important factors for successful therapy [19]. It is important to reduce side effects and motivate patients to adhere to treatment in favor of optimizing treatment responses [20]. Due in part to the side effects, the adherence to interferon-based HCV treatment was limited, resulting in dosage reduction and sometimes discontinuation of therapy, which led to the frequent virus breakthrough [21]. Historically, the most predominant side effects have consisted of “flu”-like symptoms: fatigue, myalgia, fever, insomnia, and weakness [22]. Although up to two-thirds of patients complained of fatigue, it is important that the clinician distinguishes it from severe anemia, depression, or other metabolic disorders [23]. The “flu”-like symptoms were usually easily managed and did not lead to treatment discontinuation. On the other hand, cytopenias, particularly anemia, were the most troublesome side-effect, causing drug-dose reduction and early treatment discontinuation [24]. In addition, patients with HCV had other conditions that required treatment with medications that could cause hematologic toxicities. For that reason, a multifaceted approach was required, such as pretreatment screening, cardiac, and hematologic consultations when necessary, frequent laboratory monitoring, and dose reductions [25]. Erythropoietin and blood transfusions, as well as aggressive RBV dosage reductions, are effective for managing anemia [26].

Various types of dermatologic manifestations, such as dry skin and pruritus, have been reported during anti-HCV therapy. Dermatologic side effects seriously affect the skin barrier, quality of life, and sleep. A break in the skin can be the point of entry for a bacterial infection. Injection site reactions from interferon-based therapies may occur typically characterized by

local tenderness, erythema, and itching [27]. It is wise to eliminate any unnecessary medications before HCV therapy and to recommend good skin hygiene. For patients who develop drug-related rash, use of topical antipruritics or systemic antihistamines can be helpful, but sometimes dermatology consultation is required for further management [28].

Some of the most frequently reported gastrointestinal symptoms include nausea and dysgeusia. Patients may minimize nausea by taking RBV with food; however, antiemetics may be needed [25]. Dysgeusia is treated by sipping water frequently. To maintain salivary flow and oral hygiene, oral ointments and mouth washes are used [29]. Anal discomfort, with or without diarrhea, may respond to barrier creams and hemorrhoidal ointments. Patients presenting with a rectal bleed and abdominal pain should be worked-up for ischemic colitis, which can be diagnosed by CT scan with contrast or colonoscopy [30].

Psychiatric effects of HCV therapy are relatively preventable through symptom monitoring, frequent visits to assess clinical improvement, the use of selective serotonin reuptake inhibitors, and IFN dose reduction when needed. Patients who develop severe depression should be taken off HCV therapy because suicide has been reported on combination therapy [31]. The health care provider should observe symptoms that could be related to depression, such as sleep disturbance, irritability, and decreased memory. Early consultation with a psychiatrist is of great importance for defining a psychiatric diagnosis, selecting a treatment, and educating the patient about treatment expectations [32].

There are many ways a health care provider can help the patient manage side effects of the treatment. A gentle modification of behavior or routine medical therapy is often the first step, followed by dose reduction or adding additional medications. Patients are advised to rest when required and to maintain a regular daily schedule. Also, encouraging physical activity may help maintain emotional balance and promote energy levels [33]. Maintaining hydration is important in boosting a sense of well-being. Providing a support network, such as availability of nurses and an after-hours telephone health link, improves adherence to treatment and patient satisfaction. Additionally, the right timing and the adequate injection of the PEG-INF injection can be helpful [29].

Patient quality of life (QOL) during HCV treatment affects medication adherence [34], which is why it is necessary to think broadly about treatment management. In a study conducted by Manos et al., serious financial consequences of the HCV treatment (job loss, decreased work hours, difficulty paying for medications) were reported by 34.8% patients [35]. Over half of the patients reported difficulty attending social functions. When asked to rank how helpful different types of support might be for future patients undergoing treatment, the most highly ranked options were more frequent provider contact by telephone and peer support availability. Overall, patients were more satisfied with a care provided by a nurse or clinical pharmacist rather than by physicians. Others have reported frustration with communication among physicians and communication between the patient and the physician [36]. Furthermore, a common desire among patients was access to multidisciplinary services [35]. Communication quality is impacted by the time limitation of providers. To address such limitations, some healthcare systems rely on nurse practitioners and physician assistants to care for patients with hepatitis C [37]. The importance of nurses in patient QOL during HCV treatment and

their support has been rated highly [38]. Mental health providers are also helpful to maintain HCV treatment adherence, and a pilot study suggests effectiveness of the weekly telephone meetings with a mental health professional [39]. Other studies and guidelines suggest that interdisciplinary, integrated care models can help optimizing HCV treatment [40, 41].

In conclusion, the treatment of HCV should be undertaken by physicians with a broad clinical knowledge. Close clinical follow-up of patients is needed for early recognition and appropriate management of most of the side effects. Prescreening patients for potential clinical problems is crucial part of side effects anticipation which leads to involving specialists in a timely manner. The HCV provider is able to address side effects and monitor the efficacy of the regimen when patient visits twice monthly, at least in the beginning of therapy. Moreover, successful adherence to treatment can be enhanced by a strong support network, which includes specially trained hepatitis nurses and a multidisciplinary team consisting of pharmacists, counselors, and social workers.

5. Approach considerations in the IFN-free treatment era

The protease inhibitor boceprevir was approved in 2011, followed by the approval of telaprevir [42]. A third protease inhibitor, simeprevir, was approved in 2013 and is recommended as a part of combination therapy for chronic HCV infection. More recently, NS5B polymerase inhibitor sofosbuvir has emerged as an important component of currently recommended regimens [43]. In 2014, the FDA approved an all-oral regimen of simeprevir plus sofosbuvir for treatment-naïve or treatment-experienced patients [44]. DAAs are effective regardless of race, gender, or HIV status [45, 46]. They have few side effects, short durations of treatment, and high SVRs. Therefore, DAAs have the potential to lower mortality, improve QOL, and reduce long-term costs of complications in HCV infected individuals [47]. This is why every patient with chronic HCV infection should be considered for antiviral treatment with DAA agents, even if previous interferon-based therapy has failed [48].

There are certain settings where limited access to medications forces health practitioner to decide which patient should be treated first. In circumstances like this, practitioners rely on evidence-based medicine and guidelines. Treatment for CHC is based on guidelines from the Infectious Diseases Society of America (IDSA) and the American Associations for the Study of Liver Diseases (AASLD) [49]. Recommendations are evidence based and are constantly updated as new data from peer-reviewed evidence become available. The guidelines propose that treatment priority should be given to those with the most urgent need. The recommendations include the following:

1. The highest priority for treatment should be given to the patients with advanced fibrosis, compensated cirrhosis, and severe extrahepatic hepatitis, as well as liver transplant recipients.
2. Patients with high priority for treatment are the ones at high risk for liver-related complications and severe extrahepatic hepatitis C complications.
3. Certain subgroups of HCV patients, such as men who have high-risk sex with men, active injection drug users, incarcerated persons, and those on hemodialysis are patients whose risk of HCV transmission is high, and in whom, HCV treatment may result in a reduction in

transmission. In those patients, treatment decisions should balance the anticipated reduction in transmission versus the likelihood of reinfection.

Although antiviral therapy for CHC should be determined on a case-by-case basis, treatment is widely recommended for patients with elevated ALT levels who meet the following criteria [50]: older than 18 years, positive HCV antibody and serum HCV RNA, compensated liver disease, adequate hematologic and biochemical indices, willingness, and adherence to treatment, without contraindications.

In Europe, EASL Recommendations on Treatment of Hepatitis C assist physicians and other healthcare providers in the clinical decision-making process by providing information about the current optimal management of patients with acute and chronic HCV infections [51]. The recommendations have been based on evidence from existing publications and presentations at international meetings and the expert personal experiences. According to EASL, all treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV, who have no contraindications to treatment, must be considered for therapy. The treatment must be available without delay in patients with significant fibrosis or cirrhosis, including decompensated cirrhosis; patients with clinically significant extrahepatic manifestations (e.g., symptomatic vasculitis, mixed cryoglobulinemia, nephropathy, and non-Hodgkin B-cell lymphoma); patients with HCV recurrence after liver transplantation; patients with concurrent comorbidities who are at risk of a rapid evolution of liver disease (non-liver solid organ or stem cell transplant recipients, diabetes); and individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, hemodialysis patients, incarcerated individuals) [51].

Prior to initiating DAA therapy, patients should undergo a thorough pre-treatment evaluation, which includes identifying the genotype of hepatitis C, evidence of cirrhosis, and previous treatment. Comorbid physical or psychological conditions should be optimized before commencing therapy because it will improve compliance. Evaluation for advanced fibrosis is recommended for all persons with HCV infection [49]. Another important consideration before starting therapy is the possibility of drug-drug interactions, as well as severe renal impairment [48].

Treatment of chronic HCV infection has two goals: to achieve SVR and to prevent progression of cirrhosis, hepatocellular carcinoma, and decompensated liver disease which can lead to the liver transplantation [49]. Patients who achieve an SVR experience numerous health benefits, including a decrease in liver inflammation levels, a reduction in the rate of progression of liver fibrosis [52], and reduced symptoms and mortality from severe extrahepatic manifestations [53]. Patients with normal liver function tests after SVR can be managed as if they had never been infected with HCV. Individuals who have failed to achieve SVR must be given an opportunity to pursue further therapeutic options [48].

6. Approach considerations in the near future

Currently, access to treatment for HCV is limited, with only a minority diagnosed patients, and even fewer assessed are initiated on treatment [54]. HCV therapy has the potential to

ensure individual and health benefits, but high prices have stopped access to HCV therapy, even in high income countries and to people with advanced liver disease. If DAAs are to stop HCV-related mortality and decrease the global burden of HCV infection in the coming years, current HCV treatment rates of 1% to <5% must be increased [55]. Treating patients with fibrosis will decrease morbidity and mortality of HCV, but unless patients without advanced liver disease are treated too, the epidemic of HCV will continue [56].

7. Conclusion

Key desirable characteristics of the HCV therapy include high efficacy, tolerability, pan-genotypic activity, short duration, oral administration, affordability, and fixed-dose combination. The major reasons for limited treatment access are the cost, complexity, and limited effectiveness of treatment, as well as lack of access to reliable and affordable diagnostics. The improved safety profile and improved efficacy across genotypes of the new DAAs make the pre-treatment screening simple. In the future, HCV treatment could be initiated immediately after confirmation of infection and the presence of viremia, with only an initial assessment of the stage of liver disease. Future development of pan-genotypic regimens with minimal side effects that will be available at an affordable price holds the greatest potential for expanding access to treatment to all HCV patients.

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