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Mini Review

New Challenges (and Opportunities) in the Era of New Hepatitis C Treatments

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Abstract

Treatment of chronic hepatitis C infection is rapidly evolving. Two new drugs, simeprevir and sofosbuvir, have just been approved by the US Food and Drug Administration. Numerous treatment regimens that are more tolerable and more efficacious are in late phase of drug development and are coming to the clinics. In this background, new issues, challenges and opportunities face both the treatment providers as well as patients with chronic hepatitis C infection.

It is estimated that 4 million individuals are infected with chronic hepatitis C in the United States [1]. Many of those infected individuals are not aware of their infection. Approximately up to 80% of acute hepatitis C infections will end up as chronic infections that are largely asymptomatic until the development of chronic liver disease complications. Approximately 5-25% of chronic hepatitis C infection will develop cirrhosis in 25-30 years but risk is higher among older, obese, immune suppressed and alcoholic individuals. In those who have cirrhosis, there is a risk of hepatic decompensation and hepatocellular carcinoma [3,4]. Successful treatment of chronic hepatitis C (sustained virologic response, SVR), equivalent to a cure of the infection, results in a decrease in the risk of developing liver-related complications [5]. Thus, a sustained virologic response after HCV treatment particularly in those with advanced liver fibrosis is highly desirable.

Treatment of chronic hepatitis C infection is currently experiencing a revolution. There is a rapidly evolving treatment landscape affecting clinical decisions at the bedside. The developments of interferon- and ribavirin- free treatment regimens are now a reality, a concept that was uncertain a few years ago. Until more recently, pegylated interferon alpha and ribavirin have been the standard treatment for all genotypes of HCV infection [6]. In 2011, the first HCV NS3/4A protease inhibitors – telaprevir and boceprevir, improved treatment efficacy in HCV genotype 1 infections, the most common HCV genotype in the United States. These two FDA-approved direct acting antiviral agents (DAA), have increased SVR rates among HCV genotype 1 infections by approximately 30% compared to those treated with pegylated interferon and ribavirin. SVR rates of approximately 65 to 75% among treatment naïve patients and relapsers and a relatively smaller improvement in SVR rates among prior partial responders and null responders, particularly those with advanced fibrosis and cirrhosis, have been reported [7]. Both of these HCV protease inhibitors are used in combination with pegylated interferon and ribavirin for 6 to 12 months depending on on-treatment response termed "response-guided therapy." Thus, the associated side effects of interferon and ribavirin remain along with the significant pill burden and frequent dosing schedule. In addition, some of the side effects like the anemia and neutropenia can be exacerbated by the addition of HCV protease inhibitors [8,9]. Treatment discontinuation rates of up to 40% have been reported in real world settings with lower SVR rates compared to registration trials of these drugs [10]. A better and much more tolerable therapy remains to be desired.

Many new HCV drugs are being developed and studied in various combinations with the goal of eliminating interferon and ribavirin.Once a dream for HCV-infected individuals, is now a reality for some. There have been a significant number of promising therapies including fixed-dose combination of an all-oral and ribavirin-free regimens with excellent SVR rates presented in what seems to be in an endless series of updates in multiple scientific meetings. At least 20, if not more new HCV drugs are in advanced development (Table 1) [11]. Two new HCV drugs -- sofosbuvir, a nucleotide NS5B polymerase inhibitor and simeprevir, a second generation NS3/4A inhibitor have been approved by the US Food and Drug Administration for the treatment of infections due to HCV genotype 1 (sofosbuvir and simeprevir) and genotypes 2,3 and 4 (sofosbuvir) [12,13]. Both drugs are recommended to be taken orally on a daily basis in combination with pegylated interferon and ribavirin for HCV genotype 1 and 4 (sofosbuvir) and genotype 1 (simeprevir) infections. A total treatment duration as short as 12 weeks with -(sofosbuvir pegylated interferon and ribavirin for HCV genotypes 1 and 4 infections, and sofosbuvir and ribavirin combination for HCV genotype 2) is recommended even for those with

Table 1: New HCV Direct Acting Antiviral Agents in Advanced Development.

HCV Direct Acting Antiviral Agent	Phase	Genotype Specificity
NS3/4A Protease Inhibitor		
Boceprevir	Approved	1
Telaprevir	Approved	1
Simeprevir	Approved	Pan-genotypic except 3
Faldaprevir	III	1(1b>1a)
Danoprevir	II	1 and 4
Asunaprevir	III	1
ABT450	III	1
Vaniprevir	II	1
NS5B Inhibitor (Nucleoside)		
Sofosbuvir	Approved	Pan-genotypic
Mericitabine	II	1 and 4
VX135/ALS220	I/II	Pan-genotypic
NS5B Inhibitor (Non-nucleoside)		
ABT333	III	1
Deleobovir	II/III	1
VX-222	II	1
BMS-791325	II	1
NS5A Inhibitors		
Daclatasvir	III	1 (1b>1a)
ABT 267	III	Pan-genotypic (mainly 1)
Ledispasvir	III	1
ACH2928	I	Pan-genotypic (mainly 1)
IDX719	II	1,2,3 and 4
Cyclophilin Inhibitors		
Alisporivir	II/III	1,2 and 3
SCY635	II	1

advanced fibrosis and compensated cirrhosis. On the other hand, an all oral regimen of sofosbuvir and ribavirin for 24 weeks in patients with HCV genotype 3 and those interferon-ineligible with HCV genotype 1 infections is recommended. In addition, sofosbuvir has been approved for those with HIV co-infection, a group considered to be hard-to-treat population. Simeprevir taken together with pegylated interferon and ribavirin for first 12 weeks and additional 12 weeks of pegylated interferon and ribavirin (naïve and relapsed on prior interferon and ribavirin), or additional 36 weeks of pegylated interferon and ribavirin (prior non-responder to interferon and ribavirin) is recommended. A baseline testing for the presence of NS3 Q80K polymorphism in HCV is advised. Presence of this mutation substantially decreases treatment response with simeprevir and in this case, alternative treatment should be considered. Looking into a not too distant future, the following drugs are in late stages of drug development and hopefully will be approved by FDA in 2015 – faldaprevir (protease inhibitor), daclatasvir (NS5A inhibitor) and asunaprevir (NS5A inhibitor).

New opportunities, lessons and challenges come with new HCV therapies. Once again, the opportunity to treat patients in the clinic with the next wave of new HCV drugs (sofosbuvir and simeprevir) has arrived. Previous treatment challenges like significant pill burden and frequent dosing schedule is expected to go away for those infected with HCV genotype 1. For the many infected with HCV genotype 2 and 3, there will not be a routine interferon use. Lessons have been learned in the search for better HCV therapies. For example, the HCV-infected population who need treatment the most – cirrhotics, liver transplants and HIV co-infected were previously excluded from the early clinical trials of telaprevir and boceprevir that may have impaired early utilization of these therapies in this subpopulation of HCV patients. Now, even prior to FDA approval of sofosbuvir and simeprevir, clinical studies in this subpopulation have been presented in many recent scientific fora with promising results. Along with great anticipation for new HCV therapies is a new perspective in how clinicians utilize tools in the evaluation of chronic liver disease due to hepatitis C infection.Liver biopsy, for the most part, is not commonly used anymore to make treatment decisions given the current treatment landscape. Non-invasive markers to diagnose cirrhosis in HCV infection is now playing a greater role [14]. It remains unclear how IL28B genotype testing, a marker of interferon responsiveness, will be used in the era of all-oral treatment regimen [15]. The clinicians who amidst the avalanche of scientific information, will have to make a clinical decision and hope for the best outcome for their patients. With the new opportunities to treat HCV infections come many different challenges.Some of the questions being asked and debated by experts today include: *Do I need treat my patients now, or can they wait for new better therapies? Which regimen is the best for my patients among all these therapies? What will be the most cost-effective way of treating HCV infection?* There are several factors that affect this decision including those related to the provider, the patient and the payer i.e. insurance company. The provider's ability to put his clinical decision in perspective of rapidly changing treatment options is important. Risk stratifying patients to cure HCV infection depending on the stage of chronic liver disease while minimizing, if not avoiding harm should be the goal. The risk of hepatic decompensation among those individuals with cirrhosis is real. The potential unintended consequence of failing a novel all oral DAA therapy, for example, may conceivably result in HCV drug resistance and preclude the use of better future therapies. Comparative treatment trials similar to HIV therapies may prove useful in guiding clinicians. Patients, many of whom depend on their physicians' advice, should be educated and be informed of their treatment options including, if available, participating in clinical trials of promising therapies so they can make an informed decision regarding HCV treatment. The cost and expense of (re)treatment may be an issue with insurance companies and third party payers and can affect treatment decisions in HCV care.Both the CDC and the US Preventive Services Task Force now recommend hepatitis C screening among those born between 1945-1965 (birth cohort screening) [16,17]. With more people being screened for chronic hepatitis C infection, more diagnoses will be made and more patients will need to be treated. Therefore, the ability to provide care for these patients cannot be overemphasized. Current hepatitis C treatment providers are, for the most, part limited to hepatologists, some gastroenterologists and infectious disease specialists. Depending on how simple and acceptable HCV treatment will be in the future, a significant number of primary care physicians may be able to provide necessary treatment to help address this demand for hepatitis C providers.

The outlook for patients with chronic hepatitis C is very bright. New, effective and better treatment options are available now and more will be available soon. With this exciting development in HCV therapy, old problems will be solved, new lessons will be learned and new challenges will be faced by many providers and patients alike.

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