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Editorial

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Evolving Therapies for the Treatment of HCV Viral Hepatitis

Hepatitis is a general term referring to inflammation of the liver, a condition that can result from infection with a virus, bacterium, or a parasitic organism, or alternatively from noninfectious causes such as alcohol, drugs, or autoimmune disease. Viral infections are responsible for over half of all diagnosed cases of hepatitis. While a number of viruses replicate in multiple organs including the liver, hepatitis viruses are defined as those that show a primary tropism for the liver. These viruses include types A, B, C, D, E, and F (not confirmed). Of these, types A, B, and C are the most common. Infection with these viruses can lead to acute disease characterized by symptoms of nausea, abdominal pain, fatigue, malaise, and jaundice. Severe cases of acute viral hepatitis can rapidly progress to acute liver failure. Additionally, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection can lead to chronic infection. Patients who are chronically infected with HBV or HCV have a high probability of developing cirrhosis and/or hepatocellular carcinoma. Chronic hepatitis carriers remain infectious and can transmit the disease for many years postinfection.

While the population impact of HBV infection has long been appreciated (it is still the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma worldwide), the epidemiology of HCV infection and its significance to world health has only become clear in the last two decades.[1] HCV infection is extremely widespread and has put an enormous burden on the world healthcare system. In July of 2013, the World Health Organization (WHO) reported that HCV is found worldwide with some countries having chronic infection rates in excess of 5% of the population (Egypt, for example, has the largest known burden of HCV infection with a 10% incidence in persons aged 15 to 59).[2] Seroprevalence data suggests that as many as 185 million people are infected worldwide and consequently are at risk of developing cirrhosis and/or hepatocellular carcinoma. It is estimated that an additional 3 to 4 million people will be infected with HCV every year with 350,000 people dying from HCV related liver disease annually. The virus is most commonly transmitted through (1) receipt of contaminated blood products or organ transplants, (2) contaminated syringes and needle-stick injuries in health care settings, (3) injection drug abuse, and (4) transmission to a neonate by a hepatitis C infected mother.

Complete eradication of a pathogenic virus is the goal of antiviral therapy, but this has often proven to be difficult if not impossible to achieve. However, a sustained virologic response (SVR) to treatment for HCV infection, as measured by viremia, has been shown to significantly reduce liver-related morbidity, as well as all-cause mortality in chronically infected patients. Until 2011, the standard of care was treatment with a combination of interferon alpha given once weekly as a subcutaneous injection and ribavirin given orally twice daily for 24 to 48 weeks. Fewer than half of those infected with genotype 1 virus (there are six genotypes of virus, 1 through 6, with multiple subtypes in each genotype) were cured by this treatment regimen, and many patients were ineligible or unable to tolerate it. Clearly, additional treatment options were needed. Two direct acting antiviral agents, boceprevir and telaprevir, that selectively target the virally encoded NS3/4A protease received United States FDA regulatory approval in 2011. Both of these drugs are indicated in combination with pegylated interferon and ribavirin, and their inclusion in the treatment regimen led to higher rates of SVR. However, because of sequence variability in the NS3 protease across genotypes, these drugs are only indicated for the treatment of genotype 1. By mid-2012, additional direct acting antivirals targeting the NS3/4A protease, the NS5B polymerase, and the NS5A protein (involved in formation of the viral replicase complex) were in various stages of clinical development. In late 2013, the United States Food and FDA-granted approvals for two additional HCV drugs. Sofosbuvir, a first-in-class NS5B inhibitor, was approved in combination with pegylated interferon alpha and ribavirin for patients infected with genoytpes 1 and 4, and in combination with ribavirin alone for patients infected with genotypes 2 and 3 (use of the drug in combination with ribavirin alone is also allowed in patients infected with genotype 1 who are interferon ineligible). The NS3/4A protease inhibitor, simeprivir, also received approval for treatment of patients infected with genotype 1 virus, including patients with cirrhotic livers, in combination with pegylated alpha interferon and ribavirin. On the basis of clinical results with the approved drugs and on data emerging from additional drugs in late stage clinical trials, there is considerable optimism that an interferon alpha and ribavirin sparing combination can be identified that has pangenotypic activity and that has a high SVR, even in patients with advanced liver disease.

Despite these considerable advances in the treatment of chronic HCV infection, more research and development effort is needed. Clinical experience with the treatment of HIV, HBV, and various herpesvirus infections has shown that over time multiple drugs and drug combinations are necessary for continued control of viral replication and continued interruption of the pathogenic course of disease. These additional drugs and combination regimens were needed due to the pharmacokinetic and metabolic variability found in larger populations, as well as the impact of various coincident medical conditions on drug efficacy. Also, although the development of drug resistance and treatment breakthrough has not yet proven to be as big of an issue for HCV as it has been for other viruses, there is no guarantee that it will not become an issue as drugs are more widely used. In addition, the global burden of HCV infection is mostly found in Africa, the Middle East, and Asia where HCV genotypes 4, 5, and 6 are common. These genotypes are relatively uncommon in the West where pivotal treatment trials for the new drugs were conducted. Consequently, it is not clear if the currently approved drugs or the drugs currently under development will be effective in these

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populations. It is also true that the current standard of care treatments that are available in developed nations are not affordable in these regions, and more affordable medicines will be required.

As a consequence of this, the editors of *ACS Medicinal Chemistry Letters* thought it would be timely to put together a special issue of the journal dedicated exclusively to the current research and patents in this very important area. I was pleased to serve as the Guest Editor for this special issue.

George Painter, Guest Editor

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AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

REFERENCES

(1) Hanafiah, K. M.; Groeger, J.; Flaxman, A. D.; Wiersma, S. T. Global Epidemiology of Hepatitis C Virus Infection: New Estimates of Age-Specific Antibody to HCV Seroprevalence. *Hepatology* **2013**, *57* (4), 1233−1341.

(2) World Health Organization. Hepatitis C Fact Sheet No. 164; updated July 13, 2013. who.int/mediacentre/factsheets/fs164/en/.