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The Ongoing Debate Of Who To Treat With Chronic Hepatitis C

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Abstract

Chronic hepatitis C virus (HCV) infection is a major cause of cirrhosis and hepatocellular carcinoma worldwide[1] and the leading indication for liver transplantation in the adult United States population.[2] Although the incidence of chronic HCV infection is declining, the number of deaths is projected to rise over the next decade.[3] Hence, the major reason for treating chronic HCV infection is to mitigate the morbidity and mortality associated with the infection but also to alleviate patient symptoms and to prevent person-to-person transmission. Successful eradication or virological cure is possible and a reduction in liver-related outcomes has been demonstrated in patients with advanced liver disease who achieve this desirable endpoint.[4–6]

Keywords

Hepatitis C Virus; Natural History; Cost; Treatment

Despite these facts, only 7% to 11% of patients are treated based on an analysis conducted by the Division of Viral Hepatitis at the Centers for Disease Control and Prevention of two large datasets containing more than 18,000 subjects.[7] This is partly because treatment of chronic HCV infection has been challenging for both the patient and healthcare provider. Available regimens were complex to administer, of long duration, associated with substantial toxicity and moderately effective in that only ~50% of patients with the most common genotype of the virus-HCV genotype 1 responded. Patients had to be carefully selected for therapy. Only those with more advanced liver disease based on a liver biopsy with a reasonable likelihood of responding to treatment, with limited comorbid conditions and who could be expected to tolerate treatment were recommended for therapy.[8] All others, particularly those with mild disease, were advised to be followed perhaps with a repeat liver biopsy every five years to reassess the need for treatment. Consequently, many infected individuals were ineligible to receive therapy due to contraindications or if treated, had to prematurely discontinue therapy due to intolerance or opted not to receive therapy preferring to wait for the promise of safer, more effective treatment.

The other reason for the low treatment rate was related to our understanding of the natural history of chronic HCV infection. Liver disease is thought to progress slowly in the majority of patients, particularly if certain factors that can accelerate fibrosis progression are absent

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such as older age at infection, male sex, heavy alcohol consumption, obesity, insulin resistance and co-infection with HIV or HBV.[9–11] It is estimated that approximately 25% of individuals will progress to cirrhosis or decompensated liver disease over a period of 25–30 years.[9] Therefore, treating a patient early in the course of their disease would expose them to unnecessary toxicity and complications from treatment with unproven benefit on outcome of their liver disease.

In this issue of JAMA, Butt and Colleagues report rather provocative results from an analysis of a VA database which suggests that after infection with HCV, patients may experience a more rapid progression of liver fibrosis and accelerated time to development of cirrhosis than previously thought. However, once cirrhosis develops, the disease appears to stabilize and the development of hepatic decompensation in the first 10 years is infrequent.

Does this mean that we should change our approach to treatment and recommend therapy for patients earlier in the course of their disease? Before addressing this question, we need to revisit the current state of therapy. Therapy of chronic HCV infection is at a watershed moment. Multiple oral agents have been developed that specifically target key viral proteins necessary for the viral lifecycle and tested in different combinations for variable durations ranging from 12 to 24 weeks.[12–17] These new regimens are highly effective and increase the response rate from approximately 50% to >90%. More importantly, these new treatment regimens have become much simpler to administer, safer and more tolerable with minimal side effects.

So given this interesting data on natural history coupled with the prospect for more effective and safer therapies, effectively removing many of the previous barriers to therapy, one may make a strong argument for treating everyone. Why delay therapy when we are unsure how best to monitor untreated patients and accurately identify patients who are at risk for disease progression thereby allowing the disease to advance which may adversely affect future response rates and increase the risk of complications from the disease? In response, there are several epidemiological studies indicating that most individuals with hepatitis C will die with rather than from their infection.[18–20] Furthermore, evidence of the benefits of treating patients with mild disease is lacking and the new impediment to treatment is now the cost of therapy. The recently approved oral agents sofosbuvir, a HCV polymerase inhibitor, costs $84,000 dollars for a 12-week course equating to about $1,000.00 per pill[21] and simeprevir, a HCV protease inhibitor, $66,000 for 12 weeks or approximately $786.00 per pill.[22] The price of these new drugs has not escaped the attention of policy makers or insurers. A recent analysis conducted for the Pharmaceutical Care Management Association estimated that the cost of new HCV drug therapies will increase 2015 federal spending on the individual Medicare Part D program by approximately $2.9 billion to $5.8 billion.[23] This is equivalent to a 6% to 11% increase in federal Part D spending or approximately $100 to $200 per Medicare Part D beneficiary per year.[23] Officials for the State Medicaid plans have cautioned that the cost of the new treatments will place substantial financial burden on Medicaid budgets.[24] Major news organizations reported that three states Colorado, Illinois and Pennsylvania, have already implemented specific criteria to permit use of the drugs only in patients with the most advanced stage of liver disease while limiting treatments for

patients with a history of drug use and alcohol abuse.[25,26] So the bottom line is even if we wanted to treat everyone we simply could not afford to.

It is somewhat ironic that with more effective and safer therapy we are still debating who to treat but this is the current state of affairs surrounding treatment of hepatitis C. So clinicians are faced yet again with the situation of having to prioritize who should receive treatment but for different reasons. Who are the patients that are most likely to benefit from therapy? Patients with the greatest risk for disease progression i.e. those with advanced liver disease, patients co-infected with HIV or HBV and patients who have received a liver transplant who are at risk for recurrent cirrhosis or graft failure should be given priority.[27] Not many would argue with this list. A somewhat more controversial group are individuals who have a high risk of transmitting the infection these include men who have sex with men, active injection drug users, incarcerated persons and persons on long-term hemodialysis.[27] Treatment in this case serves a dual purpose; it benefits the individual as well as society. Practitioners have been reluctant to treat these persons because of their high risk for re-infection. For the time being the decision to treat other patients should be individualized. Patients who are not treated should be closely monitored for disease progression using liver biopsy, non-invasive testing or a combination of the two. However, this is not an exact science and it is possible some patients may progress despite our best intentions. Until the issue of cost associated with these new treatments is resolved, the debate on who should receive treatment will rage on.

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