E-FILED
Thursday, 08 January, 2015 09:31:48 AM
Clerk, U.S. District Court, ILCD

January 5, 2015

Andrew Batey, MD

Gastroenterologist/Hepatologist,

Director Digestive Health Center,

Carle Hospital, Urbana, IL

Chronic Hepatitis C Management

Introduction:

Chronic hepatitis C is the most common blood-borne viral infection leading to chronic disease in the US. It is estimated that 1.3% of the population (3.2 million to 5 million) are chronically infected[1]. As the virus primarily causes damage to the liver leading to fibrosis (scarring), over time some patients develop progressive liver fibrosis leading to cirrhosis (when the liver is completely replaced with scars). This process may take up to 20 to 30 years in some patients however there are factors that can accelerate fibrosis, prominent among which is chronic alcohol use and co-infection with HIV. Once cirrhotic, reversal is extremely difficult even if the virus can be eradicated with treatment. With development of complications from liver cirrhosis, liver transplantation becomes the only viable treatment to prolong life for appropriately selected patients. Chronic hepatitis C is now the leading indication for liver transplantation and leading cause of death in patients who are con-infected with HIV.

Screening:

Since this is a blood-borne infection, all individuals who have used intravenous (IV) and intranasal recreational drugs sharing needles and straws should be screened with hepatitis C antibody test. This is also true in individuals who had been transfused with blood, blood products or had solid organ transplantation before June in 1992, when universal screening for the virus was adopted by all blood banks in the US. Target screening in special populations like incarcerated individuals, veterans, HIV or hepatitis B infected patients are also recommended. In one study of 330,000 - 860,000 incarcerated individuals, a positive rate of 16 – 41% was found[2]. The most inclusive and provocative recommendation for screening though was issued by the Centers for Disease Control and prevention (CDC) last year indicating the need to screen **all individuals** born between **1945 and 1965** (the so called baby boomers) irrespective of the presence or absence of the aforementioned risks as a vast majority (about 75%) of the patients with the disease fall into this age group[3].

Evaluation:

A positive screening test should be followed with a more confirmatory HCV RNA molecular test. Once confirmed, a genotype test is recommended followed by determination of degree of fibrosis either non-invasively for instance with the FIBROSCAN device or invasively with a liver biopsy which remain the gold standard. Further evaluations should attempt to identify other coexisting liver diseases, extra hepatic manifestations of disease, screening for HIV and hepatitis B and other baseline blood tests.

A screening test result return in days however a confirmatory molecular test may take 1 to 2 weeks. FIBROSCAN is an office based test that takes 5 minutes which unfortunately is still not widely available. A liver biopsy therefore continues to be used to stage fibrosis. It typically takes about a week to schedule and another week or so for a pathologist to review and interpret the findings on biopsy. This done, another visit is then scheduled to discuss the results and treatment options which may take about 2 weeks. In summary therefore, from the time of a positive screening test to completion of the work-up to be fully informed about a decision to treat or not, varies from 1 to 3 months.

Treatment:

Recent advances have made for a very rapidly evolving treatment regimens for hepatitis C with discovery of highly effective direct acting antiviral agents (DAAs). Up until October last year, the FDA had approved only the use of all the oral agents available in combination with parenteral pegylated interferon (PEG-IFN) for the most common (about 70%) hepatitis C genotype of 1. While the response rates in terms of cure were modest (about 60 -75%), the treatment regimens were long (6 months and more) but more importantly, side-effects from PEG-IFN were a hindrance and led to discontinuation of therapy is some patients.

In October, 2014, the **first all oral combination** therapy of DAAs (Sofosbuvir and Lepipasvir) was approved by the FDA for treatment of patients with chronic hepatitis C genotype 1 based the ION trials[4.] An earlier all oral regimen used by experienced physicians for some patients; a combination of Sofosbuvir and Simeprevir based on the COSMOS trial was also approved by the FDA[5]. Finally, a third regimen which is made up of a four drug combination was approved a few weeks ago (December, 2014). This consists of Paritaprevir, Ritonavir, Ombitasvir (3-D) and Dasabuvir to be used with or without Ribavirin[6]. Any of these three all oral regimen have been shown to achieve over 90% cure rates with very minimal side-effects and shorter duration of therapy for the most part, 12 weeks but occasionally in advanced diseases especially previous treatment failures up to 24 weeks.

The availability of these medicines have created exciting times for physicians interested in treating this disease particularly those that have been around for a while looking back to where we had come from, dismal cure rates with very toxic medicines used in the past. The drawback now is **money** as these combination therapies are expensive costing $84,000 to $150,000 to treat one patient.

Recommendations:

Patients may be waiting from 1 to 2 months to be seen followed by another 1 to 3months to complete the work up for treatment as earlier stated. Treatment duration for 12 weeks (3 months) for most patients and a final 12 weeks (3 months) to determine for cure would make for a total of approximately 9 months. The first recommendation therefore is that unless an individual is going to be incarcerated for at least 1 year, initiation for evaluation for therapy should not be made.

Once enough time is determined, the next step would be to proceed with the work-up as indicated above. At completion of the work-up, it is my opinion that ALL patients (assuming no contraindications to medicines) should be considered for therapy irrespective of the stage of fibrosis. Indeed this was a consensus statement issued in 2002[7]. This recommendation is also supported by the following reasons;

1. The very high cure rates with minimal side-effects of therapy.
2. Ease of administration of medicines and little supervision.
3. Decrease of the disease burden to society.

The major argument against this approach is the cost. A previous suggestion was to restrict therapy only to the sickest patients, which are those with more advanced fibrosis and cirrhosis. Studies after studies have shown that the patients without fibrosis (or with milder fibrosis) are more likely to respond to therapies than those with cirrhosis. The problem with patients with advanced fibrosis and cirrhosis is that even after they are cured of hepatitis C, the burden of the damage remains, mainly with risk for developing liver cancer, as such they will continue to require close follow-up for the rest of their lives. Treating patients even before they develop more advanced fibrosis therefore makes sense.

Suggestion to reduce cost:

Administrators of the correctional centers should collectively bargain with pharmaceutical industry to getting the best price of medicines as the costs are not fixed. Sending patients to be evaluated and treated by experienced physicians may also reduce cost as there are instances in select patients where the disease can be treated even for a shorter duration of 8 weeks thereby further reducing costs.

References:

1. Edlin B, Shu M, Barron-Vaya Y. Five million Americans infected with HCV: a corrected estimate. Presented at AASLD 2005, Nov
2. Centers for Disease Control. Prevention and control of infections with hepatitis viruses in correctional settings: recommendations and reports. *Morb Mortal Wkly Rep*. 2003;52(RR-1): 1-33. 11-15, San Francisco, CA. Oral Presentation 44.
3. Centers for Disease Control and Prevention (CDC);cdcgov/knowmorehepatitis
4. (a). Mangia A, et al. EASL 2014. Abstract O164. 2. Afdhal N, et al. N Engl J Med. 2014;370:1889-1983.
   (b) Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.
   (c) Kowdley KV, et al. N Engl J Med. 2014;3701879-1888.
5. Jacobson I, et al. AASLD 2013. Abstract LB-3. Lawitz, et al. EASL 2014. Abstract 165.
6. (a). Feld JJ, et al. EASL 2014. Abstract O60. Reproduced with permission. 2. Feld JJ, et al. N Engl J Med. 2014;370:1594-1603. 3. Zeuzem S, et al. EASL 2014. Abstract O1. 4. Zeuzem S, et al. N Engl J Med.
   (b) Poordad F, et al. N Engl J Med. 2014;370:1973-1982.
   (c) Andreone P, et al. Gastroenterology. 2014;[Epub ahead of print].
   (d) Ferenci P, et al. N Engl J Med. 2014. 22;370:1983-1992.
7. NIH consensus statement on management of hepatitis C. Gastroenterology 2002;123:2082-2099