AASLD 2015: Clinical Impact of DAAS -- Referrals for Liver Transplants Drop

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The number of hepatitis C-related referrals for liver transplantation has declined significantly since the introduction of HCV direct-acting antivirals (DAAs), according to 2 U.S. studies presented at the recent 2015 AASLD Liver Meeting in San Francisco. But a related French study found that only 16% of candidates with hepatitis C and decompensated cirrhosis were taken off the transplant list.

A retrospective analysis showed that the approval of the second-generation of DAAs was accompanied by a 23% reduction in the proportion of liver transplant referrals that were HCV-related. There was also a significant 33% reduction in the proportion of transplant referrals related to HCV that had not yet progressed to hepatocellular carcinoma (HCC). The investigators suggest their findings are early evidence of the clinical impact of DAAs.

However, another study of the impact of DAA treatment on liver transplant waiting list numbers in France found that despite improvements in liver function as a result of treatment, and a high cure rate, only 16% of transplant candidates with decompensated cirrhosis due to hepatitis C were delisted as a result of treatment.

HCV is the leading cause of referral for liver transplantation in the U.S.; approximately 45% of people who receive liver transplants in the U.S. have hepatitis C. Liver transplantation may be recommended for people with end-stage liver disease -- decompensated cirrhosis -- and for people with liver cancer where the cancer has not spread beyond the liver and tumors are still small.

Some studies have shown improvements in liver function and clinical symptoms of liver disease in people with cirrhosis after sustained virologic response to treatment of hepatitis C with direct-acting antivirals. Whether this benefit extends to people in need of liver transplants, and whether treatment can allow the liver to heal sufficiently for a person to come off the transplant waiting list, is unclear.

Ryan Perumpail from Stanford University Medical Center and colleagues designed a retrospective study analyzing trends in referrals for HCV-related liver transplants in the period before (August 2012-October 2013) and after (January 2014-March 2015) the approval of simeprevir (Olysio) and sofosbuvir (Sovaldi), the first 2 DAAs to be widely used in interferon-free regimens. Data were obtained from the United Network of Organ Sharing (UNOS) in September 2015. Referral trends were also compared between hepatitis C patients with and without HCC.

The proportion of all referrals related to HCV declined from 35% in August 2012 to 27% in March 2015, a 23% decline. In addition, the proportion of referrals involving hepatitis C patients without HCC fell from 23% in August 2012 to 15% in March 2015, a 33% decline.

There was a significant drop in the number of non-HCC hepatitis C patients referred for transplant between August 2012-October 2013 (mean 188 per month) and January 2014-March 2015 (mean 153 per month). Overall, the proportion of non-HCC hepatitis C patients referred for transplant declined by 13%, from 66% in August 2012 to 58% in March 2015.

The investigators acknowledge that their study is limited by its retrospective design. Nevertheless, they conclude there was a significant decline in new referrals for HCV-related liver transplants after second generation HCV DAAs became available.

A second analysis, by Santiago Munoz and colleagues from Drexel College of Medicine, looked at outcomes from 5 studies which reported on post-treatment changes in liver function in people with decompensated cirrhosis on the transplant waiting list, showing the potential impact of direct-acting antiviral treatment on liver transplant availability in the U.S.

The 5 studies evaluated various combinations of DAAs in 533 people with decompensated cirrhosis, and recorded information on MELD scores before and after treatment. A MELD score of 15 or above indicates severe loss of liver function; patients with scores above 15 are judged to be in need of a liver transplant. Overall, 84% achieved sustained virological response.

The review found that MELD scores improved after treatment in 56% of participants across the 5 studies, worsened in 23%, and stayed the same in 20%. Nearly half (47%) experienced an improvement of 3 points or more in their MELD scores after treatment. In addition, 48% saw their Child-Pugh class improve from C to B, while 35% improved from B to A.

Patients with pre-treatment MELD scores close to the threshold tended to experience improvements in MELD score that reduced their need for a liver transplant more quickly than those with MELD scores in the 20-25 range. People with MELD scores in the 15-19 range fell below 15 after an average of 5 months, whereas for those with MELD scores in the 20-25 range a decline below 15 took an average of 10 months.

Applying these findings to a model of the liver transplant waiting list population, Munoz and colleagues estimated that "DAA-induced MELD reduction down to the threshold of transplant benefit would occur in 592-993 listed HCV patients during the first year."

Furthermore, somewhere between 213 and 515 donated livers could be reallocated to other people on the waiting list during the first year if between 60% and 90% of people with decompensated cirrhosis on the waiting list were treated with direct-acting antivirals and had improvements in MELD score to the degree seen in the 5 studies already conducted.

However, a third study, looking at a French national cohort of 183 people with hepatitis C awaiting liver transplantation and treated with DAAs between November 2013 and June 2015, found that despite a median baseline MELD score of 9.7, only 18% were taken off the waiting list after treatment, due in part to the high proportion of patients with liver cancer on the list (106 patients).

More than a third (36%) of patients with decompensated cirrhosis had a complete response to treatment after an average of 68 weeks follow up, and 57% of those with HCC. In this study a complete response -- as distinct from sustained virological response -- was defined as total bilirubin <35 mμmol/L, prothrombin time >50%, albumin >35g/L, no ascites, and no hepatic encephalopathy.

A change in Child-Pugh class to less severe cirrhosis was classified as a partial response; in this cohort 28% of those with decompensated cirrhosis and 13% of those with HCC had a partial response.

Presenting the findings, Audrey Coilly of from Hopital Paul-Brouss said that it may be "asking too much in the short term" for liver function to improve substantially among people with decompensated cirrhosis. She remarked that in the era of interferon-based treatment, some data suggest that it took up to 5 years after successful treatment for the portal pressure gradient to fall in people with cirrhosis, and that longer-term follow up of people on liver transplant waiting lists is needed to assess the effects of treatment.