Expected increase in prevalence of HCV-related cirrhosis and its complications in the United States: No effect of current antiviral treatment coverage?

Augmentation attendue de la prévalence de la cirrhose liée au VHC et de ses complications aux États-Unis : la couverture des traitements actuels n’a-t-elle pas d’effet?

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Summary  Davis et al. projected the future prevalence of chronic hepatitis C (CHC) and its complications in the United States, using a multicohort natural history model with a tree model. First, the model predicted that in 2010 many patients have already progressed to F4, including to decompensated cirrhosis and HCC. Second, the model emphasized that cirrhosis and its complications are most common after 60 years old, regardless of when the infection occurred. Finally, the model showed that current treatment patterns will have little effect on the incidence of the complications hepatitis C.

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Commentary

With a prevalence of 4 million patients with chronic hepatitis C, the United States has begun to feel the damage caused by this infection. Davis et al. have projected the future prevalence of chronic hepatitis C (CHC) and its complications in the United States using a model. Modeling is useful in predicting the future consequences of HCV disease, based on all available data on the clinical and epidemiological characteristics of HCV as well as the distribution of infections in the past. Multicohort models involve the stratification of past HCV infections according to factors known to be associated with the natural history of HCV, such as age at infection, gender and disease duration. Past HCV infections are followed through the natural history model from infection to death. Disease outcomes are evaluated for the last 60 years and the upcoming decades considering no treatment on one hand, and treatment penetrance ranging from 0 to 100% in 2010 on the other hand.

Assuming that there was a peak in past HCV infections in 1989 and that this population was not treated, the total

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doi:10.1016/j.gcb.2010.09.004
number of patients with cirrhosis will reach a peak in 2020, while liver decompensation and cancer will continue to increase for another 10 to 13 years. In 2010, 24.8% of HCV-infected patients have already progressed to cirrhosis, including decompensated cirrhosis and hepatocellular carcinoma (HCC). Treatment of all the infected patients in 2010 could reduce the risk of cirrhosis, hepatic decompensation, liver cancer and liver-related deaths by 16, 42, 31 and 36% by 2020. However, current treatment patterns will have little effect on these complications.

Most of the previous models for the United States did not take into account heterogeneity in HCV progression due to cofactors [1—3]. Davis et al. took into account the effect of cofactors such as age, disease duration and gender on the progression of HCV showing the importance of multiple cohort modeling. The originality of Davis et al.’s paper is that he used TreeAge Software to construct the model and provided all the details as well as most of the data in supplementary files. This should make reproduction of the model easy for readers in other countries.

Progression of HCV is defined in a model represented as a figure and a tree model. Discrepancies were noted between the two presentations. Acute hepatitis C can resolve, evolve to fulminant hepatitis, progress to chronic hepatitis, or end in death. Chronic hepatitis was modeled through the stages of fibrosis, disease complications and death. Recovery from acute hepatitis, fulminant hepatitis and chronic hepatitis are defined according to age at infection, like the progression of fibrosis and the development of HCC. Moreover, the progression of fibrosis also depends on the patient’s current age (≤50 vs >50) and gender. Transition rates for the progression of fibrosis are mostly based on the pooled rates from a meta-analysis reported by Thein et al. [4]. In contrast to the latter analysis, Davis et al. stated that the progression of fibrosis increases after the age of 50. Moreover, Davis et al. indicate the possibility that some patients may progress more slowly or may not move at all according to tunnel states. In tunnel states, the transition probabilities depend on how long an individual has been in the state. Unfortunately, the authors do not give the value of the tunnels but only mention that they adjusted the transitions of fibrosis to accommodate tunnel states so that overall rates remain consistent with those of Thein et al. [4]. As a result, data are missing to reproduce the model.

Age- and gender-specific all-cause mortality is derived from standard US mortality tables [5]. Antiviral treatment is not modeled because of lack of data and non-standardized practices in the United States. Therefore the authors estimate the potential impact of treatment by considering treatment penetrance (0—100%) in 2010 with a sustained viral response of only 40 to 80%. However, the authors do not say whether all patients are considered candidates for treatment regardless of their stage of fibrosis (F0 to F4). The potential impact of antiviral treatment on cirrhosis and its complications is assessed for the year 2020.

Annual numbers of newly acquired HCV infections are provided for 6 age- and gender- cohorts per year from 1950 to 2030. They are generated from a previously published model that estimated the past incidence of acute HCV infection [1,6] stratified by age and gender based on the cases of acute hepatitis reported to the Centers for Disease Control and Prevention’s Sentinel Counties Study. Large sensitivity analyses have been performed varying transition probabilities for the youngest female and the oldest male cohorts as well as increasing background mortality, to show how the parameters change the outcomes. The relevant references for sensitivity analyses on background mortality, would have been Neal et al. [7] and Amin et al. [8].

The model predicted the numbers of cases in histological stages of fibrosis, decompensated cirrhosis and HCC over time. The authors emphasize that cirrhosis was found in 10% of cases in 1998 and 20% in 2006, and that the projected proportion is 24.8% in 2010, 37.2% in 2020 and 44.9% in 2030, although the total number of persons with cirrhosis is expected to peak in 2020 and slowly decline thereafter. This is a consequence of earlier peaks in the total number of chronic HCV patients (2001) and of patients with F0 (1990), F1 (1998), F2 (2005) and F3 (2012). Moreover, the number of chronic HCV patients will have decreased to below 2,000,000 in 2030 when most patients will be in advanced stages.

These results are subject to two comments. First, the distribution of histological stages by year shows that in 2010 many patients have already progressed to F4 (24.8%), including decompensated cirrhosis (in about 12% of patients with cirrhosis) and HCC (in about 1.4% of patients with cirrhosis). These patients are not the best candidates for antiviral treatment because of the advanced stage of their disease. Therefore the assumption considering treatment penetrance in 2010 would underestimate the real impact of treatment. Indeed, for example in 2002, when the combination of pegylated interferon and ribavirin became available, the distribution of patients in histological stages was quite different and shows a higher number of patients in less severe stages who are thus better candidates for treatment.

Second, the projected number of cases of decompensated cirrhosis and HCC by year may be overestimated because it does not include the impact of antiviral treatment.

The cohort analysis provides the projections for cirrhosis, decompensation, HCC and death by sub-groups according to gender, age at infection and duration of infection. This emphasizes that cirrhosis and its complications are most common after the age of 60, regardless of when infection occurred. This is important to note because this means that the age at infection which is often unknown, is not necessary to estimate the risk of complications after 60 years.

In conclusion, despite certain limitations in this model such as not taking into account the effect of current treatment on the complications of hepatitis C, Davis et al.’s paper supports extending screening and treating infected patients.

**Conflicts of interest**

SDB has received research grants from Roche and Janssen-Cilag.

**References**


