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ANALYSIS

# Is widespread screening for hepatitis C justified?

Several organisations have recommended greatly expanded screening for hepatitis C infection. **Ronald Koretz and colleagues** are concerned that no study has tested whether this will lead to net clinical benefit or harm in screened populations

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In 2012, the advent of new treatments for hepatitis C led the US Centers for Disease Control and Prevention (CDC) to recommend screening of everyone born during 1945-65 since it estimates that three quarters of all people infected are in that age cohort.[1] Previously, the CDC had recommended testing for people at high risk, such as intravenous drug users, transfusion recipients before 1992, and patients on haemodialysis. Cohort testing was also endorsed by the US Preventive Services Task Force (grade B recommendation),[2] which under the Affordable Care Act mandates insurers to provide the screening without any charges to the individual.[3] In April 2014, the World Health Organization called for expanded screening,[4] and in October 2013, New York State went further, passing legislation making it mandatory for hospitals to offer testing to all patients born in 1945-65.[5]

The recommendations have received strong support from many experts.[6-8] Widespread screening has been hailed as an opportunity to save hundreds of thousands of lives worldwide. Advocates often cite the substantial prevalence of hepatitis C infection, the burden of end stage liver disease, and now the availability of seemingly highly effective treatments to support expanded screening. However, since most people infected with hepatitis C never develop symptoms and will die from other causes, exposing them to the harms of treatment with no possible benefit might outweigh the benefits for the minority who develop end stage liver disease (decompensated cirrhosis or hepatocellular cancer). We discuss the natural course of hepatitis C infection, examine the treatment strategies, and suggest how we can determine whether widespread screening for hepatitis C is warranted.

## Incidence and natural course

The incidence of hepatitis C (consisting of newly recognised cases of both acute and chronic infections) in the US fell steeply from 1989 (291 000 cases) to 2010 (17 000).[9] However, after changes in CDC's case definition in 2010-11, and a campaign to expand testing, the number of new cases rose 45%; the CDC acknowledges that this was at least partly due to "increased ascertainment."[9] Around 170-200 million people worldwide are estimated to have antibodies to hepatitis C virus, about 350 000 of whom die each year.[10] We estimate that this translates into 125-150 million people with active infection.

At least 2.7 million people are infected with hepatitis C virus in the US,[11 12] and around 16 000 people each year die or have liver transplantations because of the disease.[9 13] This suggests that <0.6% of infected patients will die of liver disease or be transplanted each year.

The main concern of patients with chronic hepatitis C infection is developing end stage liver disease. Retrospective studies of the natural course of hepatitis suggest that end stage liver disease is common and that it takes about 20 years to develop cirrhosis and 30 years to develop liver cancer.[14-17] However, such series are usually composed of people who have a medical problem and are thus a sicker subpopulation of the people with chronic hepatitis C infection (referral bias). Furthermore, the total number of infected patients from which they are drawn is unknown.

Patients with chronic hepatitis infection also tend to die earlier from non-hepatic causes than other people.[18] This shorter life expectancy would leave less time for the progressive hepatic fibrosis to result in end stage liver disease. Furthermore, many of the reasons that led to infection (substance misuse, other risky behaviours, blood transfusions for underlying diseases) also

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reduce life expectancy. Thus, the association between hepatitis C infection and increased risk of death from non-hepatic causes cannot be assumed to be causative.

Natural course is best determined by following an entire cohort identified at the time of infection. Several such studies have been published (see table A in appendix on thebmj.com, which presents the outcomes in the subset of people who developed chronic infection).[19-26] The risk of developing end stage liver disease is low for the first three decades of infection. Unfortunately, data on the risk beyond that point are limited. Only three studies provide data beyond 30 years, and the data are for children[23] and women[19] (both groups perhaps being at lower risk of progression) and for men in whom it was not clearly proved that the infections were chronic when diagnosed.[24] Nonetheless, these data are consistent with previously cited epidemiological data from the general population, and it is likely that 80-85% of patients with chronic hepatitis C will die from non-hepatic causes.[19-26]

Progression of hepatitis C infection is not random; ongoing use of intravenous drugs, alcohol misuse, obesity or steatosis, older age, genetic factors, and coinfection with HIV, all increase the likelihood of progression.[27] Thus there may be possibilities for non-drug interventions to prevent hepatic complications.

## Treatment efficacy

The most convincing way to establish efficacy of treatment is through well designed and conducted randomised, placebo controlled trials using clinical outcomes (morbidity and mortality). However, such trials are available only for interferon monotherapy. Ten randomised trials of interferon alfa have been conducted in patients with severe fibrosis or cirrhosis.[28] The results were disappointing, even though at the time, expert opinion advocated interferon treatment for these patients.[29]

Researchers have rationalised the use of surrogate markers (such as, sustained virological response, serum enzyme activity, and hepatic histological assessments) in trials because so few patients develop end stage liver disease (meaning trials with clinical outcomes have to be large) and it takes many years to manifest. The preferred surrogate marker is sustained virological response (defined initially as non-detectable hepatitis C virus RNA in the serum for at least 24 weeks after stopping treatment, though recently 12 weeks has been used[30]). The lack of effectiveness of interferon monotherapy in trials may be the result of the small percentage (15-20%) of patients who had a sustained virological response.

Combination therapy with pegylated interferon (peginterferon) and ribavirin leads to sustained response rates of around 50%.[31] First generation protease inhibitors telaprevir and boceprevir produce rates of about 70%.[32] Most recently, other drugs such as sofosbuvir and ledipasvir, used in various combinations, have resulted in sustained response rates above 90% in some studies, even without peginterferon,[33] and people are starting to talk about a "cure."[6]

Do high percentages of sustained response translate into long term clinical benefit? Most of the information comes from observational studies comparing treated patients who did, or did not, develop sustained virological responses. We know that those who develop a sustained response will not usually show evidence of viral RNA in other body tissues.[34-38] More importantly, they also have less liver related morbidity and mortality compared with people without a sustained response.[39-43] However, since all participants in these studies received treatment, it is likely that the differences in clinical outcomes are due to inherent differences in patients who respond or do not respond to treatment. The ability of therapy to reduce the incidence of end stage liver disease is unproved.

Patients who achieve sustained response are less likely to have the risk factors associated with disease progression[44-46] and it may be simply a marker of those who were less likely to progress even without treatment. There is some evidence to support this hypothesis. A Cochrane review of retreatment with interferon found that it modestly improved sustained response and markers of inflammation but produced clinical harm.[28] In other words, sustained response is not a valid surrogate marker for interferon monotherapy.

Sustained response rates above 90% paradoxically suggest that it will not be a good surrogate outcome for newer treatment regimens either, since most hepatitis C patients will not develop end stage liver disease and will therefore be unnecessarily treated. We need to stop separating patients infected with hepatitis C according to sustained response and think about them as those who will, or will not, develop end stage liver disease.

Sustained virological response is not a cure. Viral RNA is sometimes found in body tissues even when the serum is clear[34 37 38]; in some studies this has been found frequently.[47 48] The virus also reappears in some patients with sustained response,[49 50] and though this might be thought to be due to reinfection, at least sometimes these events represent the reappearance of the same virus.[50] Moreover, a few patients with a sustained response develop end stage liver disease.[39 40 42 51 52] In the largest observational study to assess this risk, 1001 patients with severe fibrosis (84% with cirrhosis) with sustained virological response were followed for up to eight years. During that time, 50 developed hepatocellular carcinomas, a 1% annual risk.[51] Observational studies have suggested that the annual incidence of hepatocellular carcinoma in people with compensated cirrhosis secondary to hepatitis C infection is 1.4-3.3%.[53]

Other evidence used to justify antiviral treatment is derived from non-randomised controlled studies and modelling. Non-randomised studies are plagued by confounding,[54 55] and modelling has used spurious assumptions that favour treatment (table B on thebmj.com).[18 56]

It may be that the small percentage of patients who were initially destined to develop end stage liver disease are all (or mostly) included in the small number of patients who either do not develop sustained virological responses or who go on to develop end stage liver disease in spite of a virological response.

## Harms of treatment

Claims of increased safety or tolerability of the newer treatment have been based on fewer and less severe side effects. However, the new drugs can still cause serious adverse events (resulting in persistent disability, hospital admission, or death). Some new drugs are still combined with interferon and ribavirin. Interferon can cause serious harms, including bone marrow suppression and death (4% absolute increase in all cause mortality in the HALT-C trial[57]).[28] Ribavirin commonly causes anaemia and results in leucopenia, skin rashes, gastrointestinal upset, or insomnia in 10-20% of patients.[58] The protease inhibitors can cause severe anaemia and skin rashes, including the potentially fatal Stevens Johnson syndrome.[59]

Safety data are limited for the newest drugs. However, in a trial of sofosbuvir versus peginterferon plus ribavirin, 3% of participants taking sofosbuvir experienced serious adverse events compared with 1% in the peginterferon plus ribavirin arm

(difference not significant).[60] Combination therapy with sofosbuvir plus ledipasvir with or without ribavirin, was associated with a 0.5-2% rate of serious adverse events.[61] According to a recent analysis of US Food and Drug Administration data, over one year telaprevir accounted for the single greatest number of reported severe and fatal skin reactions of any drug monitored.[62] Unfortunately, we cannot weigh the risk versus the benefit at this time because we have no data on the precise benefit (if any).

## Clinical trials agenda

Although widespread screening for hepatitis C may be a cost effective strategy for reducing the development of end stage liver disease, it may result in more harms than benefits. We need clinical trials to determine the outcomes of treatment in screen detected patients and long term harms associated with antiviral regimens, as highlighted by the US Preventive Services Task Force.[2 63]

A definitive method to evaluate cohort screening would be a randomised trial of hepatitis C testing in a large number participants from the target population (those born during 1945-65 in the US). The primary outcome would be death from liver disease or hepatocellular carcinoma. The CDC recommendations require the screening of about 60 million Americans. A trial of 120 000 participants (about 0.2% of the target population) would be expected to produce 250-500 deaths from liver disease or hepatocellular cancer, if we assume that 5-10% of deaths in this population are due to hepatic causes and the annual all cause death rate is about 1% for the 50-70 age group (0.4% at age 50 and 2.0% at age 70). In the general population, about 1.5% of deaths are due to liver disease or hepatocellular carcinoma so the study would have excellent power to demonstrate a 30% relative risk reduction in the number of deaths from liver disease or hepatocellular carcinoma in the screening arm. Secondary endpoints would be all cause mortality and the composite outcome of liver transplantation or death from liver disease or hepatocellular carcinoma. If no difference is seen between the groups after four years because of low death rates from hepatic diseases, the trial could continue for another two years. However, such low death rates would raise questions about whether the clinical problem was sufficiently large to warrant screening.

Such a large simple trial could be performed at a low cost in the US by using a simple point of entry approach.[64] People who come for medical care would be automatically asked whether they want to be tested for hepatitis C, and, if they are unsure, would be asked whether they wished to be randomised. Besides linkage to death registries, no active data collection would be needed. Care for any patients who have hepatitis diagnosed would be left to the discretion of patients and their physicians and would use therapeutic options that are currently available.

A large study is needed to collect long term data on the outcomes of patients treated with the newer drugs and their combinations. Although 171 interventional studies of new drugs for hepatitis C have been registered on clinicaltrials.gov, most have fewer than 100 participants and follow-up is short, thereby offering no insight into clinical outcomes or the sustainability of virological outcomes. The two largest trials have just over 1000 participants each and their follow-up goes only to 24 weeks after treatment. An observational study of 2800 participants who have taken boceprevir or narlaprevir is expected to complete 3.5 years of follow-up by 2016.[65]

## Conclusions

If the treatment of hepatitis C is to be scaled up to cover a large portion of the 125-150 million infected people worldwide, regulatory agencies should ensure that drugs have been evaluated by long term follow-up of clinical outcomes (not just surrogate markers) in several thousands of patients. The financial cost of treatments have been discussed elsewhere,[66 67] but given the uncertainty about the validity of the surrogate markers, the lack of evidence regarding clinical outcomes of treatment or of screening strategies, and the adverse events caused by the newer regimens, screening may be premature.

Given the converging recommendations from major organisations for widespread screening, the pressure on practitioners to adopt this policy is mounting. We have a limited window of opportunity to collect appropriate evidence on whether this is a good idea. Until then, physicians should not be pressured to enforce birth cohort screening strategies out of enthusiasm for new treatments that have not yet been shown to cause long term clinical improvement.

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**Key messages**

- The CDC and other major organisations are recommending birth cohort population screening for hepatitis C infection
- Only a minority of patients with chronic hepatitis C infection will ever develop end stage liver disease
- We cannot reliably identify those who will develop end stage liver disease
- Drug trials rely on surrogate markers such as sustained virological response, which is not a cure
- Physicians should resist screening until we have strong evidence that antiviral therapy is clinically effective and the benefits outweigh the harms

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