Clin Exp Med (2006) 6:20–26
DOI 10.1007/s10238-006-0089-4

REVIEW

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Management of patients with chronic hepatitis C infection

Received: 23 January 2006 / Accepted: 23 January 2006

Abstract Chronic infection with hepatitis C virus (HCV) is a leading cause of liver-related morbidity and mortality throughout the world. Although reliable figures regarding the global prevalence of HCV infection are wanting, it is likely that HCV prevalence will continue to increase. Injection drug use is the most important source of HCV transmission in the developed world, while unsafe therapeutic injection is an important source of transmission in developing nations. The majority of exposed individuals become chronically infected, of whom 50% develop chronic liver injury. Cirrhosis and hepatocellular carcinoma can arise in those chronically infected over a mean of 20–30 years. Despite this high prevalence and morbidity, recommendations regarding who to screen by antibody testing remain disparate. Quantitative measurement of HCV RNA and HCV genotyping is useful in predicting response to antiviral therapy. Noninvasive methods of detecting liver injury, such as serologic batteries, have not been as informative or predictable as liver biopsy. The current pharmacologic standard of care for chronic HCV infection is the combination of subcutaneous peginterferon and oral ribavirin, which yields sustained virologic response in 54%–56%. Higher rates of SVR are seen in those patients who are infected with HCV genotypes 2 and 3. As intravenous drug use remains the most important source of HCV transmission in the US and Europe, education within this group is an important preventive tool.

Key words Hepatitis C • Liver • Interferon

Introduction

Chronic infection with hepatitis C virus (HCV) is a leading cause of liver-related morbidity and mortality throughout the world. It is widely believed that the prevalence of this infection will increase substantially in the coming several decades. Since its discovery in 1989, treatment modalities have seen steady, if incremental, improvement. This review aims to detail the epidemiology, natural history, diagnosis and treatment of chronic hepatitis C.

Prevalence

Reliable figures regarding the global prevalence of HCV infection are difficult to develop, because population-based data are not available in most parts of the world. The World Health Organization reports seroprevalence data that vary widely by geography, ranging from rates around 1% in Australia, Canada, France, Germany and India,

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through rates near 2% in Japan, Italy and the United States to higher figures in China (3.2%). The highest reported seroprevalence of HCV is in Egypt, with an astounding rate of 22% [1]. In the US, it is estimated that approximately 1.8% of the population, or 3.9 million persons, are seropositive for HCV, of whom approximately 75% are viraemic. Prevalence varies by age and ethnicity, with the highest rate in African American men between the ages of 40 and 49. The overall prevalence of HCV in African Americans is estimated to be 3.2%, compared to 2.9% in Mexican Americans and 1.5% in non-Hispanic Whites [2].

HCV transmission

Injection drug use is the most important source of HCV transmission in the developed world, accounting for approximately 2/3 of infections in the US and Western Europe and as much as 80% in Australia [1, 3, 4]. The practice of unsafe therapeutic injection in the developing world has emerged as an important source of transmission in those parts of the world. An important example is transmission by way of contaminated reusable glass syringes in Egyptian schistosomiasis treatment programmes, leading to that nation's very high seroprevalence [5]. Blood transfusion has diminished in importance as a risk of HCV transmission in the developing world since the institution of all-volunteer donation and effective screening methods [6]. It is likely that blood products remain a significant reservoir of HCV in developing nations [7]. Sexual, perinatal and workplace transmission are much less common routes of HCV transmission [8]. Other potential, albeit controversial, exposures include tattooing and body piercing, intranasal cocaine use and high-risk sexual practices. Recognition of HCV transmission risk factors has led to a decrease in the incidence of new infections, especially in developed nations, but the prevalence of chronic HCV is expected to rise over the coming decades [2, 9].

Natural history

Acquisition of HCV is infrequently accompanied by a recognisable clinical syndrome; in fact, an acute illness, including jaundice, occurs in only 20% [10]. Following exposure, it has been estimated that only between 10% and 25% spontaneously clear the virus [10, 11]. Of those who remain infected, 50% develop chronic liver injury [12]. Population-based studies may overestimate the frequency of HCV chronicity in exposed persons. For example, in a recent small series of 46 patients, it was observed that acute infection resulted in spontaneous clearance of virus in 24 (52%) [13].

Long-term complications such as cirrhosis and hepatocellular carcinoma can arise in those chronically infected, with the mean time from infection to the development of cirrhosis averaging 21 years [14]. It has been estimated that cirrhosis develops in approximately 20% of those infected [15, 16]. Cirrhotic patients have an 18% risk of progressing to decompensated liver disease, characterised by such events as portal hypertensive bleeding, encephalopathy and ascites [17]. Age greater than 40 at the time of acquisition of infection, daily consumption of alcohol exceeding 50 g and male sex have all been identified as factors predisposing to progression of the disease [18]. Patients with HCV-related cirrhosis have a 1%–4% yearly incidence rate of hepatocellular carcinoma. Although screening of cirrhotic patients for the development of HCC is a common clinical practice, the efficacy of such an approach has yet to be demonstrated [17, 19–21].

The natural history of HCV-associated liver disease in the HIV co-infected patient has been the focus of several studies. Approximately 15%–30% of HIV-infected patients are co-infected with HCV [22]. Compared to HCV-only infected patients, the rate of spontaneous clearance of virus is lower and HCV RNA levels are higher in HIV/HCV co-infected patients [23, 24]. The rate of progression to advanced liver disease, including cirrhosis, liver failure and hepatocellular carcinoma, is accelerated in the HIV co-infected patient. This rate of progression has led to the recognition that liver disease is now the leading cause of death in HIV/HCV co-infected patients [25–28].

Screening

Although the annual incidence of new HCV infections in the US has declined from 180 000 in the 1980s to 28 000 in 1995, the overall prevalence of this blood-borne infection remains quite high, affecting 3.9 million Americans, 2.7 million of whom have chronic infection [29, 30]. Despite this high prevalence, recommendations regarding who to screen remain disparate. For instance, the United States Preventative Service Task Force recommends against routine screening of asymptomatic persons not at risk for infection. They have also not found enough evidence to recommend screening even in those people deemed to be at risk for infection, as there is limited evidence of the effectiveness of available interventions once an individual is identified as being HCV positive [31]. However, the US Center for Disease Control and Prevention (CDC) recommends that testing be performed on all persons at risk for HCV. High-risk individuals for HCV are those who have ever injected illegal drugs, persons who received clotting factors before 1997, persons who received blood or organs before 1992, persons who have received long-term haemodialysis, persons with

unexplained elevated ALT levels, healthcare workers who sustain a needlestick or mucosal exposure from an HCV-positive individual, and lastly children who are born to HCV-positive mothers. The CDC recommends against testing long-term monogamous sex partners of HCV-positive persons [30].

Serologic tests

Diagnostic tests for HCV can be divided into serological assays, which detect antibody to HCV, and molecular assays, which detect and/or quantify HCV RNA genomes. Interpretation of these test results needs to be taken in clinical context, as the positive predictive value of any test is dependent on the prevalence of infection in the population being screened. The main screening assay for detecting antibodies to HCV is the enzyme immunoassay (EIA). EIA testing is highly sensitive, but is associated with a 30%–50% false positive rate if used in a low prevalence population [32, 33]. In this situation, such as in blood banks, the recombinant immunoblot assay (RIBA) can be employed. False negatives are rare and are confined to immunosuppressed hosts, including patients on chronic haemodialysis.

Molecular tests

Detection of HCV antibody confirms exposure to the virus in a patient with a known risk factor. Qualitative measurement is useful in confirming viraemic status. Furthermore, it is important to note that 15%–25% of adults who are exposed to HCV resolve their infection. Thus it is prudent to repeat HCV RNA on multiple occasions before drawing conclusions on chronicity of infection [33]. Quantitative measurement of HCV RNA is one of several factors useful in predicting response to antiviral therapy. Viral load, especially serial measurement, is less useful in offering prognostic information concerning HCV natural history [34, 35]. A variety of tests are available commercially, offering accurate and reproducible measurement of HCV RNA over a wide range of values [36]. These tests have been standardised to IU/ml, allowing more accurate comparison between various assays.

Genotype

Multiple subtypes of HCV, denoted as viral genotypes, have been identified. These genotypes tend to have a specific geographic distribution. Genotypes 1a and 1b are the most common genotype in the United States and Northern Europe. Genotypes 2a and 2b are common in North America, Europe and Japan, whereas type 2c is most commonly seen in Northern Italy. Genotype 3a is most common among American and European intravenous drug users. Genotype 4 tends to be most common in North Africa and the Middle East, while genotypes 5 and 6 are confined to mainly South Africa and Southeast Asia respectively [37]. HCV genotyping is the most predictive parameter used in defining antiviral therapy response rate. Although interferon response rates have also been found to be dependent on the patient's age, body weight, absence of advanced fibrosis or cirrhosis, and pretreatment HCV RNA levels, genotype 1 and 4 have been consistently shown to be most strongly associated with a lower likelihood of sustained viral response compared to genotypes 2 or 3 [38–40].

Liver biopsy

Because not all persons infected with HCV develop clinically significant liver disease, it is of importance to assess disease severity in any individual patient. Noninvasive methods of detecting liver injury have not been as informative or predictable as the gold standard, liver biopsy. Neither serum aminotransferase levels [41] nor HCV RNA levels [36] are associated with the degree of liver injury and are therefore not reliable predictors of liver disease in patients with HCV. Examination of liver histology allows determination of both inflammatory grade and fibrotic stage of liver injury. The fibrosis score allows identification of patients most at risk of developing cirrhosis and contributes to the prediction of response to therapy [36, 42]. The presence of inflammation, fibrosis and steatosis are key histologic features whose presence is predictive of progression to cirrhosis [43]. Despite its accuracy and current standing as the standard of care, liver biopsy has its flaws. None of the available modalities for obtaining the biopsy: percutaneous, percutaneous with ultrasound guidance, transjugular and laparoscopic, is free of potential serious risk to the patient [43]. Because approximately 1/50 000 of the liver is sampled with each biopsy, sampling error can occur. An adequate quantity of liver tissue reduces such sampling error; current recommendations to repeat biopsy in untreated individuals at regular intervals are a further attempt to address this limitation [44–47].

Noninvasive tests of liver fibrosis

In order to avoid the low but measurable risk of liver biopsy, as well as diminish the effects of sampling error, noninvasive

markers of disease are under development. A rubric as simple as AST to platelet ratio index (APRI) is able to predict advanced fibrosis (>1.5) and cirrhosis (<2.0) with relative accuracy [48, 49]. Newer tests have incorporated serologic measures in order to maximise sensitivity and specificity for liver fibrosis. These proprietary batteries combine measurements of macromolecules such as α2 macroglobulin, α2 globulin, γ globulin, apolipoprotein A1, γ glutamyltranspeptidase, haptoglobin and total bilirubin [50]. Some studies have identified the use of these markers as reliable predictors of liver fibrosis [50–52] while others have found the techniques to be less useful [53]. Other noninvasive techniques, including an ultrasound-based assay of "liver stiffness" have yet to be validated as useful predictors of liver fibrosis in chronic HCV infection [54].

Decision to treat

The decision on whether to treat a patient with chronic hepatitis C infection is a complex one involving analysis of both patient and viral factors. Because currently available antiviral therapy is associated with response rates of about 55%, it is imperative to recommend treatment especially to those with the highest risk of progression to cirrhosis and decompensated liver disease. This prediction is an inaccurate one, so it is appropriate to cast a wide net, offering treatment to those who present at least a moderate risk of progression during their lifetime, and best able to tolerate the sometimes difficult course of antiviral therapy. Patient age, gender, medical comorbidities, alcohol intake and likely compliance with therapy are as important as viral load, genotype and liver histology in making this assessment.

Watchful waiting

In those patients with a long period of chronic infection combined with no more than minimal necroinflammatory activity on histological assessment, and liver enzymes that are normal or near normal on repeated determination, simple observation without treatment may be elected. How best to monitor those patients being managed by so-called "watchful waiting" is a matter of controversy. Some investigators recommend periodic measurement of liver biochemical profile. The Consensus Development Statement issued by the NIH in 2002 supports recurrent biopsies, noting, "in general, a baseline assessment of liver histology offers a valuable standard for subsequent comparisons. However, the appropriate interval for subsequent evaluations is yet to be determined" [55]. These caveats being presented, it should be stated that all patients should be considered as candidates for antiviral therapy. Although lab testing, liver biopsy and drug therapy are expensive, cost/benefit analysis places HCV therapy in the bargain category when compared to many commonly accepted medical practices [56].

Standard treatment regimens

The current pharmacologic standard of care for chronic HCV infection is a combination of subcutaneous peginterferon and oral ribavirin. There are two formulations of this long-acting interferon which have roughly comparable effectiveness rates. In general, response rates are higher in those patients with genotypes other than type 1, weigh less, are younger, are Caucasian and have less fibrosis on liver biopsy [57]. Treatment success is usually implied by achieving a sustained virologic response (SVR), defined as lack of detectable virus in the serum 6 months following a treatment course. In registration trials peginterferon/ribavirin resulted in a SVR of 54%–56% [38, 39]. Retrospective analysis has suggested response rates in excess of 60% in those patients who are able to take greater than 80% of their recommended dose of therapy for more than 80% of the recommended duration of treatment [58]. Unnecessary prolongation of treatment in those patients destined to be viral nonresponders can be facilitated by measurement of viral load early in therapy [59]. The current standard time for such measurement is at 12 weeks of treatment, but earlier "stopping rules" are under investigation [35]. Higher rates of SVR (76%–82%) are seen in those patients who are infected with HCV genotypes 2 and 3, even when using somewhat lower ribavirin doses for a more abbreviated treatment course [38, 39, 60].

Treatment of relapsing and nonresponding patients

In practice, about half of those treated for HCV will have virologic relapse once interferon-based therapy is completed, or will not have had a significant response to therapy at all. With each new development in HCV therapy, this population, of whom the nonresponders are more resistant, is offered treatment, usually with around 20% response rates. Currently, investigations focus on switching peginterferon formulations [61], higher dose peginterferon [62], daily dose unmodified (nonpegylated) interferon [63], additional, potentially synergistic agents [64], and low-dose "maintenance therapy." A large, federally funded trial in the US comparing 4 years of low-dose peginterferon in nonresponders with advanced liver fibrosis will provide useful details on the latter option [65]. The development of protease inhibitors and antagonists of the HCV RNA-dependent RNA polymerase hold promise, but experience with these agents is quite limited at the time of this article. The recent

announcement that HCV can be sustained in cell culture requires further confirmation, but ought to provide a major impetus to further understanding of the virus and methods to interfere with its replication [66].

Prevention

As intravenous drug use remains the most important source of HCV transmission in the US and Europe, education within this group is an important preventive tool. In fact, it was behaviour change in this cohort that was apparently responsible for the reduction of HCV incidence in the 1990s [2]. Other potential sites for transmission reduction include the penal system, where high incidence is regularly reported [67]. Vertical transmission of HCV has been reported to occur in approximately 4% of births [68, 69], but neither type of delivery nor breastfeeding appear to be associated with transmission [70]. To date, routine screening of pregnant women for HCV infection has not been adopted in the US. When evaluating a patient newly diagnosed with HCV, it is recommended to advise against sharing of razors and toothbrushes, but to reassure regarding casual contact [55]. Sexual transmission is thought to occur, but to be inefficient compared to hepatitis B virus. Changing of sexual practices, such as the adoption of barrier methods of contraception, is not recommended in long-term monogamous couples in which one partner is HCV infected [8]. Alcohol use should be limited, given the described synergistic effects between alcohol and HCV infection [71]. Hepatitis A and B vaccination is recommended in persons chronically infected with HCV [55].

Conclusions

Since its discovery in 1989, there have been dramatic increases in the understanding of the epidemiology, natural history, diagnosis and therapy of HCV infection. Both host and viral factors figure in the complex decision of whether or not to treat chronic infection. As our therapeutic armamentarium grows and develops, the threshold for such treatment decisions is sure to change. Future research is likely to provide the clinician with a choice of antiviral tools, allowing customisation of HCV therapy, depending on severity of disease, medical comorbidities and virologic factors.

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