Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

European Association for the Study of the Liver*

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. The long-term impact of HCV infection is highly variable, from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide is estimated to be about 160 million, but most of them are unaware of their infection. The implementation of extended criteria for screening of HCV, such as targeting birth cohorts, is the subject of major debate among different stakeholders. Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention.

These EASL Clinical Practice Guidelines (CPGs) are intended to assist physicians and other healthcare providers, as well as patients and other interested individuals, in the clinical decision-making process by describing the optimal management of patients with acute and chronic HCV infections. These guidelines apply to therapies that are approved at the time of their publication. Two protease inhibitors (PIs) have completed phase III development for patients infected with HCV genotype 1, and are currently registered for use in Europe and elsewhere. Therefore, these EASL CPGs on the management of HCV infection have been updated to include guidance on the use of these two drugs, and will be updated regularly based on approval of additional new therapies and clinical experience with them. Also, substance users are increasingly considered as a treatable patient group at risk. The EASL CPGs have been updated in this respect. The preceding HCV CPGs were published as recently as 2011 [1]. These updated CPGs have built upon the earlier published work, so much remains unchanged. In particular, dual therapy remains the standard of care for patients with genotype non-1, and for some patients with genotype 1 infection. The authors of the current CPGs acknowledge the work undertaken by Professor Craxi and the authors of the 2011 CPGs which forms the basis of the current revision.

Context

Epidemiology

It is estimated that approximately 160 million individuals, i.e. 2.35% of the world population, are chronically infected with HCV [2]. Current estimates are that between 7.3 and 8.8 million persons are infected with HCV in the European Union, i.e. twice as many as an estimate made in 1997 [3]. Overall, HCV prevalence across Europe ranges between 0.4% and 3.5%, with wide geographical variation and higher rates in the south and the east [4–6].

HCV is a positive strand RNA virus, characterized by high sequence heterogeneity. Seven HCV genotypes, numbered 1 to 7, and a large number of subtypes have been described [6]. Genotypes and subtypes (which are identified by lowercase letters), differ among themselves by about 30% and 20% of their sequences, respectively. Genotype 1 is the most prevalent genotype worldwide, with a higher proportion of subtype 1b in Europe and 1a in the USA. Genotype 3a is highly prevalent in the European population of people who inject drugs (PWID). This group is currently experiencing an increasing incidence and prevalence of infections with HCV genotype 4. Genotype 2 is found in clusters in the Mediterranean region, while 5 and 6 are rare in Europe [7]. The novel genotype 7 was identified in patients from Canada and Belgium, possibly infected in Central Africa [8]. The identification of HCV genotypes and subtypes is not only of epidemiological interest, but it determines the type and duration of antiviral therapy, including the risk of selecting resistance-associated variants during therapy.

Up to the 1990's, the principal routes of HCV infection were blood transfusion, unsafe injection procedures, and intravenous drug use (IDU). Taken together, these routes are estimated to be responsible for approximately 70% of chronic cases in developed countries. Currently, however, screening of blood products

Received 5 November 2013; accepted 5 November 2013
Contributors: David Mutimer (Coordinator), Alessio Aghemo, Helmut Diepolder, Francesco Negro, Geert Robaeys, Stephen Ryder, Fabien Zoulim.Reviewers: Markus Peck, Antonio Craxi, Michael Fried, Stefan Zeuzem.
* Correspondence: EASL Office, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel.: +41 22 807 0360; fax: +41 22 328 0724.
E-mail address: easloffice@easloffice.eu
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; BMI, body mass index; BOC, boceprevir; BT, viral breakthrough; CPGs, Clinical Practice Guidelines; CYP3A4, cytochrome p450 3A4; DAA, direct-acting antiviral; DVR, delayed virological response; EIA, enzyme immunoassays; EPO, erythropoietin; eRVR, extended rapid virological response; EVR, early virological response; G-CSF, granulocyte colony stimulating factor; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDU, intravenous/injecting drug use; IFN, interferon; IU, international units; LSM, liver stiffness measurement; LT, liver transplant; OST, opiate/opioid substitution treatment/therapy; PegIFN/RBV, pegylated interferon-α and ribavirin; PI, protease inhibitor; PWID, people who inject drugs; RVR, rapid virological response; SCAR, severe cutaneous adverse reaction; SVR, sustained virological response; TSH, thyroid stimulating hormone; TVR, telaprevir.

ELSEVIER

for HCV by means of enzyme immunoassays (EIA) and nucleic acid testing has virtually eradicated transfusion-associated hepatitis C. Similarly, in the developed world, new HCV infections are infrequently related to unsafe medical or surgical procedures. Spread among the PWID community – facilitated by sharing paraphernalia, unstable housing, frequent cocaine use, and history of imprisonment – now accounts for the vast majority of incident cases in developed countries. High coverage of combined harm reduction programs (e.g. opiate substitution treatment and needle exchange programs) may reduce HCV incidence in the PWID community, and some modelling studies suggest that implementation of HCV treatment may even reduce transmission within this population [9]. Other invasive behaviours, such as tattooing or acupuncture with unsafe materials, are also implicated in occasional HCV transmissions. The risk of perinatal and of heterosexual transmission of HCV is low, while male homosexual activity has become an important transmission route in Western countries [10]. On the other hand, the situation is quite different in resource-poor countries, where lack of public awareness and continuous use of unsafe medical tools still account for a considerable proportion of new HCV infections.

Natural history and public health burden

Acute hepatitis C is rarely severe, and symptoms occur in 10 to 50% of cases. In Europe, HCV infection is responsible for about 10% of cases of acute hepatitis [11]. The incidence of acute HCV infection has decreased and is now about 1/100,000 per year, but this figure is probably an underestimate because it mainly refers to symptomatic patients. Progression to persistent or chronic infection occurs in about three quarters of cases, is influenced by the *IL28B* genotype, and is associated with chronic hepatitis of a variable degree and with variable rates of fibrosis progression. Only exceptionally does infection clear spontaneously in the chronic stage. Chronic hepatitis C proceeds towards cirrhosis over several decades. On average, 10 to 20% of patients develop cirrhosis over 20–30 years of infection [12]. In a meta-analysis of cross-sectional studies of HCV-infected PWID, the 20-year cirrhosis prevalence was 15% [13]. Once at the cirrhotic stage, the risk of developing HCC is approximately 1 to 5% per year. Patients diagnosed with HCC have a 33% probability of death during the first year after diagnosis [14].

In Europe, and dependent on the relative proportion of patients with hepatitis B virus (HBV) infection in the same geographical area, the prevalence of anti-HCV antibodies among patients with cirrhosis ranges from 11 to 61% [15]. Similarly, the prevalence of anti-HCV antibodies in patients with HCC ranges from 18 to 64% [15]. Overall, the standardized mortality rate in anti-HCV-positive persons ranges from 1.6 to 4.5, and was as high as 25 in a recent study from Scotland [16]. It has been estimated that, in countries where injecting drug use (IDU) is the major risk factor for HCV infection, 20 to 25% of deaths among HCV-infected individuals are from liver disease and 15 to 30% are from drug-related causes, although the attributable risk of death varies and is age-related [17].

In addition to the healthcare burden associated with HCV monoinfection, Europe has a significant population that is HCV/HIV co-infected. Though they represent a small proportion of all HCV-positives, they tend to have more advanced liver injury and (to date) have exhibited disappointing response rates to antiviral therapy.

Hepatitis C progression to cirrhosis is highly variable, depending on the presence of cofactors capable of accelerating the fibrotic process. Proven cofactors for fibrosis progression include older age at infection, male gender, chronic alcohol consumption, obesity, insulin resistance and type 2 diabetes, and immunosuppression (such as that occurring after solid organ transplantation and in untreated HIV infection). Importantly, despite slow HCV disease progression over the initial 20 years of infection, advancing age may accelerate fibrosis progression [18]. Tobacco smoking may increase inflammation and accelerate fibrosis [19]. Similarly, daily cannabis use has been associated with more advanced liver fibrosis, though recently published data have questioned this association [20]. Coffee consumption is associated with lower inflammatory activity, less advanced fibrosis and reduced risk of developing HCC [21–23]. For all of the above reasons, a mainstay of HCV management is the modification of cofactors. An additional consideration is the fact that many of these cofactors also reduce the rate of response to interferon (IFN)-based therapy.

The current standard of care and developing therapies

The primary goal of HCV therapy is to cure the infection, which is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of life-threatening complications, albeit at a lower rate, even after viral infection has been eradicated. The infection is cured in more than 99% of patients who achieve a sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after treatment completion. Until 2011, the combination of pegylated interferon-α (pegylated IFN-α) and ribavirin (subsequently referred to as PegIFN/RBV) was the approved treatment for chronic hepatitis C [24]. With this regimen, patients infected with HCV genotype 1 had SVR rates of approximately 40% in North America and 50% in Western Europe. Higher SVR rates were achieved in patients infected with HCV genotypes 2, 3, 5, and 6 (up to about 80%, and better for genotype 2 than for genotypes 3, 5, and 6) and intermediate SVR rates were achieved in those with HCV genotype 4 [7]. In 2011, telaprevir (TVR) and boceprevir (BOC) were licensed for use in HCV genotype 1 infection. These two drugs are first-generation direct-acting antivirals (DAAs), both targeting the HCV NS3/4A serine protease and thus referred to as protease inhibitors (PIs), i.e. both TVR and BOC must be administered in combination with PegIFN/RBV. These triple therapy regimens have proven effective for treatment-naïve and for treatment-experienced patients, including previous null responders to dual PegIFN/RBV therapy. Indications for therapy, dosages, schedules, side effects, and precautions are detailed in the sections below.

There are other DAAs at different stages of clinical development, some of them targeting HCV genotype 1 as well as other genotypes. Investigational drugs include second generation NS3/4A serine protease inhibitors, nucleoside/nucleotide and non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase, and NS5A inhibitors. Additionally, host-targeting antiviral drugs (HTAs), such as cyclophilin inhibitors, target host cell functions which are involved in the HCV life cycle. New therapeutic strategies aim towards higher efficacy, pan-genotypic activity, shortened treatment duration, easier administration and improved tolerability and patient adherence [25]. It is highly likely that IFN-sparing and IFN-free regimens with or without