Hepatitis B and Hepatitis C in 2004

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Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are among the most frequent viral infections of man and represent a major global public health problem [1, 2]. Approximately one third of the world population have serological evidence of past or present infection by HBV and 350 million people are chronically infected. Approximately 3% of the world population, 170 million people, are chronically infected by HCV. HBV and HCV related chronic hepatitis are the main causes of cirrhosis and hepatocellular carcinoma (HCC) which are responsible for a high rate of morbidity and mortality. End-stage HBV and HCV related liver disease and HCC are the main causes of liver transplantation. Indeed, in the last few years, the knowledge of the epidemiology and of the natural history of HBV and HCV infection have markedly improved. Furthermore, considerable progress has been achieved in the efficacy of therapy. New drugs and new therapeutic strategies which are currently under evaluation could further improve the efficacy of therapy in the near future.

HEPATITIS B

Epidemiology

The prevalence of HBV infection is especially high in South-East Asia and Sub-Saharan Africa where more than 8% of the population are hepatitis B surface antigen (HBsAg) chronic carriers [3]. While perinatal transmission or transmission during early childhood are

responsible for the high rate of chronic infection in Asia and Africa, sexual or parenteral exposure account for most cases in industrialised countries [4]. In most developed parts of the world, the prevalence of chronic HBV infection is less than 1%, and the overall infection rate is 5-7%. Within these areas most infections occur among high risk adult populations that include injection drug users, persons with multiple heterosexual partners, men who have sex with men, and health care workers. The risk of perinatal HBV transmission has been well described. This risk is greatest for infants born to women who are hepatitis Be antigen (HBeAg)-positive and ranges from 70-90% at 6 months of age; about 90% of these children remain chronically infected [5]. The risk of perinatal infection among infants born to HBeAg-negative mothers ranges from 10-40%, with 40-70% of these infected infants remaining chronically infected. Children born to HBsAg-positive mothers who do not become infected during the perinatal period remain at high risk of infection during early childhood.

HBV-related end-stage liver disease or HCC are responsible for over 1 million deaths per year and represent currently 5-10% of cases of liver transplantation [1, 3, 4,]. HCC is one of the most common cancers worldwide and HBV is responsible for at least 75% of this cancer [6]. The availability of safe and effective vaccines allowed wide immunization programs which resulted in the reduction of the burden of diseases caused by HBV with clear benefits in terms of prevention of cirrhosis and HCC [7].

Natural history

The natural course of HBV chronic infection is variable, ranging from an inactive HBsAg carrier state to a more or less progressive chronic hepatitis, potentially evolving to cirrhosis and HCC [8-10]. Chronic hepatitis may present as typical HBeAg-positive chronic hepatitis B or HBeAg-negative chronic hepatitis B. Apart from the molecular biology of HBV and host factors, co-infection with other hepatitis viruses, e.g. HCV, hepatitis delta virus, as well as with other not primary hepatotropic viruses, e.g. human immunodeficiency virus (HIV), can affect the natural course of HBV infection as well as the efficacy of antiviral strategies [11]. HBeAg-positive chronic hepatitis is due to wild type HBV; it represents the early phase of chronic HBV infection. HBeAg-negative chronic hepatitis is due to a naturally

occurring HBV variant with mutations in the pre-core or/and basic core promoter regions of the genome; it represents a late phase of chronic HBV infection [12]. The latter form of the disease has been recognized as increasing in many countries within the last decade and it represents the majority of cases in many countries. HBeAg-negative chronic hepatitis B is generally associated with a more severe liver disease with a very low rate of spontaneous disease remission and a low sustained response rate to antiviral therapy [12-14].

Longitudinal studies of patients with chronic hepatitis B indicate that, after diagnosis, the 5-year cumulative incidence of developing cirrhosis ranges from 8-20%. Morbidity and mortality in chronic hepatitis B are linked to evolution to cirrhosis or HCC. The 5-year cumulative incidence of hepatic decompensation is approximately 20% [15]. The 5-year probability of survival being approximately 80-86% in patients with compensated cirrhosis. Patients with decompensated cirrhosis have a poor prognosis (14-35% probability of survival at 5 years). HBV-related end-stage liver disease or HCC are responsible for at least 500,000 deaths per year.

HCC is one of the most common cancers worldwide, about 75% of which are related to chronic HBV infection. The incidence of HCC has increased worldwide and nowadays it constitutes the fifth most frequent cancer representing around 5% of all cancers worldwide. The incidence of HCC appears to vary geographically and correlates with the underlying stage of liver disease [16]. The annual incidence in HBV carriers ranges between 0.2% and 0.6%, but it reaches 2% when hepatic cirrhosis is established [17]. The oncogenic mechanism leading to liver cancer involves different pathways that are not fully elucidated. Prevention through universal vaccination has effectively decreased the incidence of liver cancer and new therapeutic agents may delay or avoid the establishment of cirrhosis. The only chance for long-term survival after HCC diagnosis is to achieve early detection through regular surveillance by ultrasound and alpha-fetoprotein determination [18]. This allows effective therapy such as surgical resection, liver transplantation or percutaneous ablation.

Therapy

Three drugs are currently available for the treatment of chronic hepatitis B: interferon-alpha, lamivudine and adefovir dipivoxil [1, 8, 19].

Conventional interferon-alpha, administered for 4 to 6 months in HBeAg-positive patients and 12-24 months in HBeAg-negative patients, induces a sustained response in only a minority of patients (10-30%) and is associated with a poor tolerability which limits duration of therapy [20, 21]. The nucleoside (lamivudine) and nucleotide (adefovir dipivoxil) analogs have the advantages of oral administration and excellent tolerance. Lamivudine, administered for 12 months, induces a sustained response in approximately 20% of the HBeAg-positive and in 5% of the HBeAg-negative patients [22-26]. Long-term therapy increases the rate of sustained response but is impaired by a high rate of resistance (50% at 3 years) [27-29]. Adefovir dipivoxil, administered for 12 months, induces a sustained response in 12% of HBeAg-positive patients [30]. Adefovir has a similar antiviral efficacy in HBeAg-negative patients [31]. The incidence of resistance to adefovir is low (6% at 3 years) [32]. Adefovir is effective on lamivudine resistant HBV [29]. It has been used successfully in patients with decompensated cirrhosis, in the pre-transplant setting or in transplanted patients developing resistance to lamivudine [33]. In patients with HBV/HIV co-infection with lamivudine resistant HBV, treatment with adefovir has a marked antiviral effect, similar to that observed in HIV negative patients [34].

Perspectives

Indeed, currently available drugs have limited efficacy and new more potent drugs or therapeutic strategies are needed. Recently, pegylated interferon monotherapy and combinations of pegylated interferon, with lamivudine and combination of adefovir and lamivudine have been assessed. The concept of combination therapy has been developed in order to increase efficacy and to decrease resistance. In addition, new nucleoside analogs are at different stages of development.

Pegylated interferon

A recent study of pegylated interferon-alpha-2a has shown a trend to a better efficacy as compared with conventional interferon with HBeAg seroconversion rates of 37% and 25%, respectively [35]. Two recent randomized controlled studies of pegylated interferon (pegylated interferon-alpha-2b in HBeAg-positive and pegylated interferon-alpha-2a in HBeAg-negative chronic hepatitis B) have

confirmed its efficacy with 36% and 43% of 24-week post-treatment response, respectively [36, 37]. Interestingly, relatively high rates of HBsAg loss, which are associated with complete and sustained remission of the disease, were observed in both studies (7% and 4%, respectively).

Combination of adefovir and lamivudine

One randomized study evaluated the efficacy of the combination of adefovir with lamivudine as compared to lamivudine alone or adefovir alone in 59 patients with HBeAg-positive chronic hepatitis B with lamivudine resistant HBV [38]. There was no significant difference in median serum HBV DNA reduction (-3.59 and -4.04 log copies/mL), rates of alanine transaminase (ALT) normalization (53% and 47%) and HBeAg loss (3 patients in each group) between the adefovir-lamivudine combination group and the adefovir monotherapy group.

Another study compared the efficacy of the combination of adefovir with lamivudine versus lamivudine used in monotherapy in 112 treatment-naive patients (107 HBeAg-positive) [39]. There was no significant difference in median serum HBV DNA reduction (-5.41 and -4.80 log copies/mL), rates of undetectable HBV DNA with polymerase chain reaction (39% and 41%) and HBeAg loss (19% and 20%) between the adefovir-lamivudine combination group and the adefovir monotherapy group. Finally, these two studies did not show superior efficacy of the combination versus each drug in monotherapy.

Combination of pegylated interferon and lamivudine

Two randomized controlled trials of the combination of pegylated interferon with lamivudine versus pegylated interferon did not show a superiority of the combination in terms of sustained response [36, 37]. However, noteworthy, higher end-of-treatment response rates were observed with the combination. In addition, in one study, the combination of pegylated interferon-alpha-2a with lamivudine decreased the incidence of lamivudine resistance [37]. Different schedules of combination need to be assessed in order to improve the efficacy.

New nucleoside analogs

A number of nucleoside analogs, with favorable toxicity profiles and a promise of increased effectiveness against HBV, are at various stages

of clinical development. Results of phase II trials of entecavir and emtricitabine (FTC) were encouraging [40, 41]. The results of phase III studies should be available soon. The results of phase II studies of telbivudine and clevudine are promising [42, 43]. Other interesting compounds are at an earlier phase of development (Table 1). These new nucleoside analogs seem to be more potent than lamivudine and adefovir dipivoxil with a good safety profile. However, one may expect that their use in monotherapy could not induce a high rate of sustained response and that long-term therapy or combination should be needed to improve efficacy and/or reduce resistance.

Lamivudine	Approved
Adefovir dipivoxil	Approved
Entecavir	Phase III
Emtricitabine (FTC)	Phase III
Telbivudine (L-dT)	Phase III
Clevudine (L-FMAU)	Phase II
L-dC, L-dA	Phase II

Table 1: Nucleoside and nucleotide analogs for the treatment of chronic hepatitis B.

HEPATITIS C

Epidemiology

The prevalence of chronic hepatitis C ranges from 0.1-5% in different countries [44-46]. It is estimated that there are 4 million in the United States and 5 million of HCV chronic carriers in Western Europe. The prevalence seems to be higher in Eastern Europe than in Western Europe [46]. In industrialized countries, HCV accounts for 20% of

cases of acute hepatitis, 70% of cases of chronic hepatitis, 40% of cases of end-stage cirrhosis, 60% of cases of HCC and 30% of liver transplants [47, 48].

The incidence of new symptomatic infection has been estimated to be 1-3 cases/1,000,000 persons annually. The actual incidence of new infections is obviously much higher (the majority of cases being asymptomatic). The incidence is declining for two reasons: (a) transmission by blood products has been reduced to near zero; (b) universal precautions have markedly reduced transmission in medical settings. Intravenous drug use remains the main mode of transmission; but, even here, the rate of transmission is diminishing due to a heightened awareness of the risk of needle sharing and, in some countries, the availability of needle-exchange programs.

In the United States, in 1999, there were 3,759 deaths attributed to HCV, although this is likely an underestimate [49]. There was a 5-fold increase in the annual number of patients with HCV who underwent liver transplantation between 1990 and 2000. The total direct health care cost associated with HCV is estimated to have exceeded $1 billion in 1998. Future projections predict a 4-fold increase between 1990 and 2015 in persons at risk of chronic liver disease, suggesting a continued rise in the burden of HCV in the United States in the foreseeable future.

In France, the prevalence of anti-HCV positive adults is estimated to be between 1.1% and 1.2%, whose 80% are viremic. Therefore, it is estimated that 400,000 to 500,000 subjects have chronic HCV infection. The prevalence varies widely in different populations: 60% in intravenous drug users, 25% in incarcerated subjects, 25% among HIV-positive patients (25,000 to 30,000 subjects have HCV/HIV co-infection) [48].

Natural history

In the last few years, the natural history of chronic HCV infection has been better understood. The progression of fibrosis determines the ultimate prognosis and thus the need and urgency of therapy. Fibrogenesis is a complex dynamic process, which is mediated by necroinflammation and activation of stellate cells [50]. The liver biopsy remains the gold standard to assess fibrosis. Scoring systems allow a semiquantitative assessment and are useful for cross-sectional and cohort studies and in treatment trials. The rate at which fibrosis

progresses varies markedly between patients. The major factors known to be associated with fibrosis progression are older age at infection, male gender, and excessive alcohol consumption [50-52]. Viral load and genotype do not seem to influence significantly the progression rate. Progression of fibrosis is more rapid in immunocompromised patients [53]. Recently, the importance of hepatic steatosis, obesity, and diabetes have been recognized and studies are in progress to understand the relationship between metabolic disorders, HCV replication and liver steatosis and progression of fibrosis [50]. There are no tests that reliably predict the rate of progression of fibrosis in an individual patient. High serum ALT levels are associated with a higher risk of fibrosis progression. On the contrary, worsening of fibrosis is uncommon in patients with persistently normal serum ALT levels [54]. However, a non-negligible proportion (about 5% each year) of these patients may present an increase of ALT levels and may develop a more progressive liver disease [55]. Serum markers for fibrosis are not fully reliable and need to be improved and validated. Liver biopsy provides the most accurate information on the stage of fibrosis and grade of necroinflammation, both of which have prognostic significance. Repeating the liver biopsy, 3 to 5 years after an initial biopsy, is the most accurate means of assessing the progression of fibrosis [2, 47].

Therapy

Combination of pegylated interferon with ribavirin

The most impressive progress has been achieved in the efficacy of therapy. With the combination of pegylated interferon and ribavirin which is nowadays reference therapy [2, 56]. A sustained virological response (SVR) is observed in roughly 50-60% of patients [57-59]. The absence of detectable serum HCV RNA 6 months after therapy, which defines the sustained virological response, may be considered nowadays as cure of HCV infection since long-term follow-up studies have shown that 97-100% of patients keep undetectable serum HCV RNA [60]. Furthermore, some studies have shown that HCV RNA is no longer detectable in the liver of sustained responders up to several years after therapy [60]. However, further studies with longer follow-up on large populations with very sensitive methods to detect HCV RNA in the serum, peripheral blood mononuclear cells and liver are

needed to confirm the eradication of HCV infection in sustained responders.

The SVR rate is as high as 90% in patients with genotype 2 or 3 and low viral load. The SVR rate is lower, 50%, in the most difficult to treat patients with genotype 1. Even if the presence of bridging fibrosis or cirrhosis is associated with a decreased chance of response, a relatively high rate of response has been observed with the combination of pegylated interferon and ribavirin (50%). The compliance with continuation of therapy with adequate dosing even increases the response rates and studies on adjuvant treatments are needed to improve clinical and haematological tolerability in order to increase compliance and the chance of response.

Treatment of non-responders

In patients who already received therapy, the chance to have a SVR with retreatment depends on the previous therapy and the type of response. In patients who relapsed after interferon or interferon-ribavirin combination therapy, the chance of SVR with retreatment with the pegylated combination is high (about 70% and 50%, respectively). Also, in non-responders to interferon monotherapy, the SVR rate is high (about 30%). In contrast, in those patients who did not respond to standard combination therapy, the rate of SVR is low (around 10%) with retreatment with the combination therapy. Interestingly, the chance of response to retreatment depends mainly on the genotype and the presence of cirrhosis.

Maintenance therapy

In non-responders to current pegylated combination therapy, the concept of maintenance therapy has been developed in the last years [56]. Many studies suggest that long-term treatment of these patients may partially decrease viral load and serum ALT levels associated with improvement in liver necroinflammation which is associated with stabilization or even possible regression of fibrosis. Therefore, maintenance therapy might decrease, at least in some partial responders, the risk of development of cirrhosis and its complications, in particular HCC. However, this hypothesis needs to be proven in prospective randomized trials and the optimal schedule and the subgroup of patients who benefit from this therapeutic strategy need to be determined.

Perspectives

Still, about half of patients do not respond or relapse after therapy and current treatment has significant side-effects and is poorly tolerated. Therefore, new more effective and better tolerated anti-HCV drugs are needed. Many drugs with different mechanisms of action are under investigation. Other types of interferon (beta and gamma) have been disappointing but their use in combination with the current pegylated treatment needs to be assessed. Interleukins (IL2, IL12 and IL10) showed poor antiviral efficacy with limitations related to their toxicity. Inosine monophosphate dehydrogenase (IMPD) inhibitors, which have potentially ribavirin-like mechanisms of action are of interest. Some of them, like mycophenolate mofetyl and levovirin did not show significant efficacy. Other IMPD inhibitors are under evaluation. Preliminary results of therapeutic vaccines are interesting but their efficacy needs to be demonstrated. Newer approaches like antisense nucleotides or ribozymes are limited by the difficulties to reach the target cells (hepatocytes).

Indeed, the enzyme inhibitors appear to be the most promising strategy. In the last years, extensive research has been conducted to elucidate the structure of HCV enzymes in order to produce specific enzyme inhibitors [61]. All of the HCV enzymes (NS2-3 and NS3-4A proteases, NS3 helicase, and NS5B RdRp) are essential for HCV replication, and are therefore potential drug discovery targets. The absence of cell culture model supporting full replication of HCV, and of convenient animal models, has limited the knowledge of HCV life cycle and the testing for antiviral molecules. The recent development of subgenomic HCV RNA replicons capable of replicating in the human hepatoma cell line, Huh 7, has been a significant advance [62]. This model (replicon) is currently the best so far for the study of HCV replication and the testing for antiviral molecules. Target based anti-HCV drugs in development are indicated in Table 1.

Recently, a NS3 protease inhibitor (BILN 2061) demonstrated its ability to inhibit NS3 protease activity in the subgenomic HCV replicon cell model [63]. In phase I studies the administration of BILN 2061 given orally, twice daily, for two days induced a decrease in serum HCV RNA level greater than one $\log_{10}$. These results constitute a major step in the field of HCV drug development since it is the first clinical evidence of an antiviral effect of an enzyme inhibitor in patients with chronic hepatitis C. Many other enzyme inhibitors, in

particular protease inhibitors, have been produced and are currently in preclinical phase or in phase I clinical trials and more are coming. Hopefully, some of these drugs will demonstrate their efficacy and safety and will be good candidates for improving, probably by using them in combinations with interferon, the efficacy of treatment of patients with chronic hepatitis C.

CONCLUSION

HBV and HCV related liver diseases represent a major public health problem. In the last few years, considerable progress has been made in the knowledge of epidemiology, natural history, factors influencing the course of the liver disease and mainly efficacy of therapy. Still important efforts are needed for the early diagnosis in order to improve the management of patients with chronic hepatic B or C.

The understanding of the mechanisms of resistance to therapy and the development of new more potent drugs and new therapeutic strategies are a challenge to decrease in the future the global burden related to chronic viral hepatitis.

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