Towards a rational treatment strategy for chronic hepatitis B

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Received: 3 April 2007 / Published online: 6 June 2007
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Chronic hepatitis B virus (HBV) infection is a serious global health issue, both because of there are currently more than 350 million affected persons and because of the possible sequelae, such as liver cirrhosis, hepatic decompensation and hepatocellular carcinoma [1]. Our long sought-after goals are to treat and to prevent disease progression in these affected individuals. The introduction of effective agents with different mechanisms of action, along with better understanding of HBV molecular biology and the natural course of chronic HBV infection in the past decades, has brought us closer to these achievable goals. However, the landscape of chronic HBV infection and its therapy have been evolving in the past 10 years. The advent and application of highly sensitive assays for HBV-DNA level and HBV genotype or mutants have allowed more detailed study of the natural history of chronic HBV infection and the impact of antiviral therapies [2]. Important data from several long-term (>10 years) follow-up studies are emerging and have shed new light on the understanding of chronic HBV infection [3–6]. In addition, the licensed drug has increased from two in 1998 to six in 2006, but the efficacy of drug therapy is still unsatisfactory. In order to help guide the healthcare providers in this evolving field, the Asian Pacific Association for the Study of the Liver (APASL) issued the first consensus on the management of chronic hepatitis B in 2000 [7]. Subsequently, the American Association for the Study of Liver

Diseases (AASLD) and the European Association for the Study of the Liver (EASL) also published their respective guidelines [8, 9]. In recent years, not only APASL and AASLD have updated their guidelines periodically and have issued their third version of guidelines [10, 11], other groups, including the US expert panel and the ACT-HBV Asia-Pacific steering committee, have also issued their respective guidelines [12, 13]. These efforts fully reflect the complexity and the rapidly evolving nature of chronic hepatitis B therapy.

All the currently available guidelines have certainly provided valuable information on each type of therapy and useful general recommendations. However, these guidelines usually leave open the first choice of drug, and general health providers have viewed these recommendations as overly general and not straightforward enough to guide their practice. In this issue of *Hepatology International*, Lau and two other experts [14] review the burden of disease, the currently available treatments, guidelines and propose a treatment strategy for a rational management of the disease. They stress that the strategy chosen must be one that considers all relevant factors for each individual patient and balances the potential benefits versus risks. More importantly, they propose an algorithm to improve clinical outcome based on the concept of sustained versus maintained remission. With this algorithm, interferon (IFN) based therapy is recommended as the first choice for well-compensated disease or immunocompetent patients aiming for sustained remission. On the other hand, long-term nucleos(t)ide analogue (NA) therapy is recommended as the first choice for decompensated disease or immunodeficient patients aiming for maintained remission [14]. EASL was the first and the only organization recommending IFN-based therapy as the first choice [9]. It is

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See related article: DOI 10.1007/s12072-007-9006-5

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noteworthy that these three authors are from Asia, Europe and US respectively, thereby suggesting that their proposal is conceptually acceptable worldwide.

While the authors have provided a balanced review and the algorithm appears reasonable and easy to follow, the cost, inconvenience of parenteral administration, side effects, and need of close monitoring of IFN-based therapy are concerns of both patients and physicians. In real life, once daily oral antiviral agent is still preferred by majority of the patients and physicians. This is well demonstrated by the fact that over 95% of the patients with chronic hepatitis B on drug therapy in Taiwan were treated with lamivudine. Many Asia-Pacific countries share the same situation, although US guidelines clearly indicated that lamivudine is not preferred for initial therapy [11, 12]. Conceivably, lamivudine resistance, rescue therapy, or sequential therapy would form a vicious cycle and eventually create serious clinical problems [15]. Before we have an “ideal” drug with a high off-therapy sustained remission but without drug resistance, perhaps we should seriously consider promoting the strategy proposed by Lau et al [14].

On the other hand, two recent long-term follow-up studies may have important therapeutic implications. One study from Korea, where >95% of patients are infected with genotype C HBV, has demonstrated that patients with persistent abnormal alanine aminotransferase (ALT) with or without hepatitis flare during the course, are associated with a significantly higher risk of disease progression, compared to those with persistently normal ALT or persistent normalization of ALT after hepatitis flares [5]. On the contrary, a study from Taiwan involving 1241 so-called inactive HBsAg carriers has shown that hepatitis reactivation occurs at a cumulative incidence of 10% at 5 years, 17% at 10 years and 20% at 20 years of follow-up [6]. These new data underline the paramount importance of monitoring patients, including the so-called inactive HBsAg carriers, so that appropriate and timely drug therapy would only be initiated in patients for whom there are clear indications.

In conclusion, the management of chronic hepatitis B is a complex and evolving issue. General health providers need straightforward and easy-to-follow guidelines. Lau et al [14] have laid the foundation towards this goal. It is anticipated that their proposal would arouse debate and

discussion in the medical and scientific community and would definitely need periodical review in light of the emerging developments.

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