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Commentary

Strategic use of lamivudine in the management of chronic hepatitis B

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ABSTRACT

Lamivudine is no longer recommended as first-line therapy for chronic hepatitis B. The same advice has been made for adefovir and telbivudine, due to their relatively weak anti-viral activity and low resistance barrier, respectively. Instead, either tenofovir or entecavir is the currently preferred anti-HBV agent, given their potent anti-viral activity and high barrier to resistance. However, these drugs are expensive and their long-term use is often unaffordable for many individuals, including most patients in developing regions, where hepatitis B is generally much more prevalent. Herein, we argue that lack of universal access to the current best anti-viral drugs for hepatitis B should not imply a suboptimal management of chronic hepatitis B which denies therapy to persons who really need it. A wise and strategic use of lamivudine may provide an opportunity to bring the benefit of therapy to large HBV-infected populations, while reducing health care costs.

The World Health Organization has traditionally tried to promote the best medical practices in regions with limited access to diagnostic tools, drugs and medical expertise. The development and implementation of cost-effective strategies to meet a medical need in developing countries is always a singular challenge, and the management of chronic hepatitis B is not an exception (Easterbrook et al., 2012). In this paper, we argue that the lack of universal access to the current best anti-viral drugs for hepatitis B, namely entecavir and tenofovir disoproxil fumarate (TDF), should not imply a suboptimal management of the disease, denying therapy to those who really need it. A wise and strategic use of lamivudine in certain individuals may also provide an opportunity to reduce health care costs, by reserving more expensive antiviral drugs for those hepatitis B patients who require treatment, but in whom lamivudine would not be sufficiently potent to suppress the viral load to undetectable levels.

1. Anti-viral therapy for hepatitis B

Lamivudine is no longer recommended as first-line therapy for chronic hepatitis B virus (HBV) infection. The same advice has been given for adefovir and telbivudine, due to their relatively weak anti-viral activity and low resistance barrier, respectively. Instead, either tenofovir disoproxil fumarate (TDF) or entecavir is currently the preferred anti-viral as therapy for chronic hepatitis B (EASL, 2009; Lok and McMahon, 2007), given their potent activity and high barrier to resistance (Gish et al., 2012). In HBeAg-positive patients, pegylated interferon-α given for 1 year may be considered as an alternative option in the subset of patients with compensated liver disease, elevated liver enzymes and low serum HBV-DNA (EASL, 2009; Lok and McMahon, 2007). TDF is the drug of choice in patients with prior lamivudine failure, since entecavir shares drug resistance mutations with lamivudine (Tenney, 2010; Zoulim and Locarnini, 2012). Whereas these principles work well for most patients with chronic hepatitis B in developed countries, a lack of resources often prevents their application in most developing regions, where HBV infection is generally much more prevalent (Abbas and Siddiqui, 2011).

The patent for lamivudine has expired, and the current cost of the drug is around 1–2 US dollars/day. Lamivudine is given as a single pill of 100 mg once a day, is very well tolerated and lacks significant drug–drug interactions (Lok et al., 2003). In contrast, tenofovir is relatively expensive (10 US dollars/day) and may occasionally produce kidney tubular abnormalities (Labarga et al., 2009; Del Palacio et al., 2012), which can lead to Fanconi syndrome (Rifkin and Perazella, 2004) or more rarely to overt renal insufficiency (Karras et al., 2003). Moreover, the long-term use of TDF has been associated with bone demineralization and increased risk of osteopenia and fractures in patients with HBV and HIV co-infection; the risk in HBV-monoinfected persons is not known (Bedimo et al., 2012). However, most patients treated with TDF achieve complete viral suppression and sustain it without selection of drug resistance (Kitrinos et al., 2013; Marcellin et al., 2008; Snow-Lampart et al., 2011).

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Entecavir is the most expensive anti-viral agent against HBV (15 US dollars/day). It exhibits a compelling safety profile and produces very rapid viral suppression (Jayakumar et al., 2012). However, its efficacy is compromised in subjects with prior lamivudine failure, in whom double dosing (1 mg/day) is recommended, as approximately 30% of patients with prior lamivudine failure may develop resistance to entecavir after 5 years of treatment (Tan et al., 2013). Moreover, in patients with advanced liver fibrosis, entecavir therapy may rarely produce lactic acidosis (Lange et al., 2009).

2. Lamivudine for hepatitis B: pros and cons

The REVEAL-B study demonstrated that the level of serum HBV-DNA is the principal marker of liver disease progression, including the development of hepatocellular carcinoma, in patients with chronic hepatitis B (Chen et al., 2006; Iloeje et al., 2006). The recognition of advanced liver fibrosis or cirrhosis, persistently elevated liver enzymes and/or high HBV-DNA levels are all compelling factors that encourage prescription of anti-viral therapy in chronic HBsAg carriers (EASL, 2009; Lok and McMahon, 2007).

The benefit of hepatitis B treatment has been well established in several studies, many of which were originally performed with lamivudine (Lai et al., 1998; Liaw et al., 2004). However, to date only one randomized placebo-controlled trial from Taiwan has demonstrated a reduced incidence of clinically measurable adverse outcomes including liver failure, hepatic decompensation and liver cancer in persons with compensated cirrhosis treated with lamivudine (Liaw et al., 2004). Other randomized trials in persons with less severe disease have shown definite benefit, including normalization of liver enzymes and improvement in hepatic inflammation and fibrosis on liver biopsy. However, persons in these trials in the placebo arm were placed on active drugs after 1–2 years and thus, long-term reduction of morbidity and mortality could not be ascertained.

The major concern using lamivudine as first-line therapy is the risk for selection of drug resistance and viral breakthrough, which occurs in up to 70% of patients by the fifth year of therapy. In fact, this occurred in roughly half of patients with cirrhosis in the randomized study of chronic hepatitis B patients from Taiwan mentioned above (Liaw et al., 2004). Progression of liver disease then resumes, and patients are again at risk for developing HBV-associated complications (Dienstag et al., 2003; Rizzetto et al., 2005). In contrast, the rates of complete viral suppression are above 90% after 5 years when treatment is initiated with either TDF or entecavir in drug-naïve patients (Tenney et al., 2009; Ono et al., 2012; Snow-Lampart et al., 2011).

In HIV infection, the major driver for selection of drug resistance is ongoing viral replication under drug pressure (Havlir and Richman, 1996). The same principle applies to HBV infection (Soriano et al., 2008). Accordingly, the risk for selection of drug resistance using nucleos(t)ide analogues is increased in chronic hepatitis B patients with high baseline serum HBV-DNA levels (such as in most HBeAg-positive carriers) and in those experiencing a slow decline in serum HBV-DNA during therapy (Liu et al., 2011).

3. Proposal for the strategic use of lamivudine

The major obstacle that limits the judicious use of anti-viral medications in resource-limited settings is the unavailability or unaffordable cost of HBV-DNA testing and of tools for liver fibrosis assessment, including performance of liver biopsy. In settings where these tools are available, we propose that a strategic use of lamivudine should rely on the lower risk of drug resistance and treatment failure in patients with relatively low HBV-DNA (<106 IU/mL) and no cirrhosis or in those with serum HBV-DNA below 105 IU/mL and ALT above twice the upper limit of normal (Chang et al., 2005; Chen et al., 2009). This is the case for many HBeAg-negative individuals in whom we suggest that lamivudine could be safely prescribed as the first choice (Fig. 1a). Lamivudine therapy is generally enough to bring HBV-DNA to undetectable levels in patients with relatively low baseline HBV-DNA levels.

In areas where HBV-DNA testing is not available, only persons with advanced liver fibrosis should be treated. Estimation of

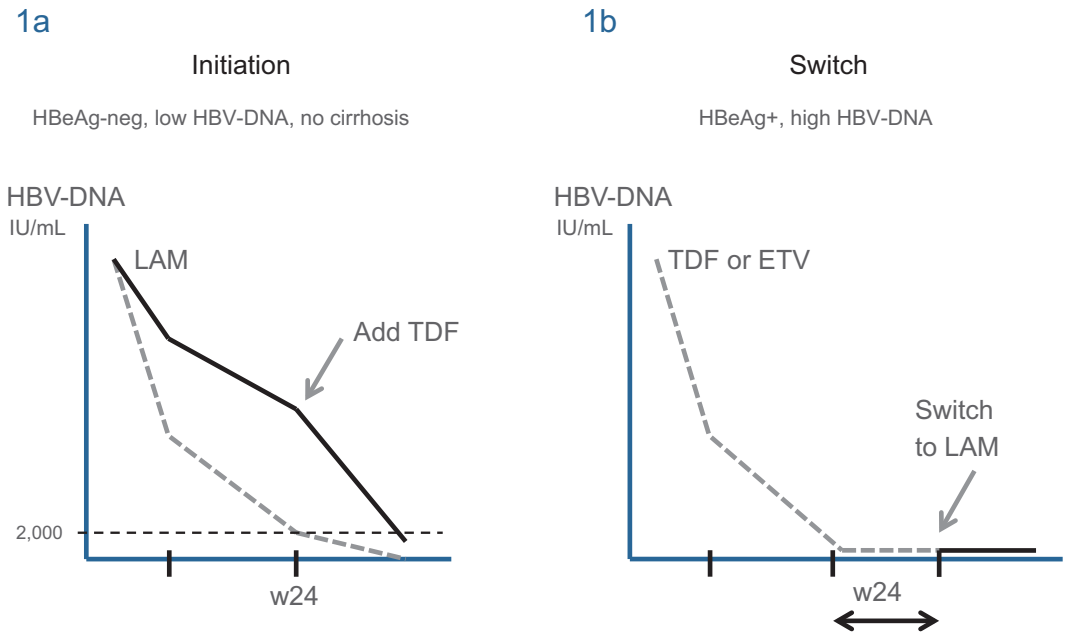

Fig. 1. Strategies for the safe use of lamivudine in chronic hepatitis B, either as initial therapy (a) or switching from other agents in patients with complete viral suppression (b).

advanced liver fibrosis could rely on liver biopsy (Metavir 3 or 4 stages), cirrhosis on ultrasound examination or simple freely available serum fibrosis indexes, such as APRI (aspartate aminotransferase/platelet ratio index) or FIB-4 (Vallet-Pichard et al., 2007). When HBV-DNA testing is available, treatment should be considered in all viremic patients, based on the REVEAL-B results. If patients achieve undetectable HBV-DNA on therapy, the risk of emergence of resistance is drastically reduced provided drug compliance is ensured. However, if lamivudine is taken irregularly, or if HBV-DNA is very high and lamivudine is unable to completely suppress viral replication, its low resistance barrier would favor the selection of resistance mutations and treatment failure. In the presence of a suboptimal response to lamivudine, the substitution of a more potent agent such as TDF may prevent selection of drug resistance and ensure the achievement of complete viral suppression (Zeuzem et al., 2009; Zheng et al., 2011). The best time for assessing viral response should be around week 24 of therapy, when a suboptimal response should be considered to be the failure to achieve a HBV-DNA level below 2000 IU/mL. In most patients with satisfactory viral response at week 24, long-term lamivudine monotherapy will work, although periodic monitoring (once, or better twice a year) would be desirable.

This "roadmap" for initiation of hepatitis B therapy (Keeffe et al., 2007; Gane, 2008) should exclude lamivudine from patients with high baseline HBV-DNA (i.e., >106 IU/mL), such as most HBeAg-positive individuals. In this subset of patients, anti-HBV therapy should begin with more potent anti-viral agents, such as TDF or entecavir, which will maximize the chances of viral response (Chang et al., 2006; Marcellin et al., 2008) and open the opportunity for switching to lamivudine once undetectable HBV-DNA has been achieved and well consolidated, i.e., during at least 24 weeks (Fig. 1b). Switching to lamivudine should then maintain complete viral suppression in most patients, reducing costs dramatically (Lui et al., 2010). However, it is important to ensure that HBV-DNA has been undetectable for a while before lamivudine switching, in order to prevent rebounds (Fung et al., 2011; Miyauchi et al., 2013). We propose empirically a minimum period of 24 weeks although studies testing this hypothesis should be encouraged.

There are at least two situations in which lamivudine use would require further caution in hepatitis B. First, patients with cirrhosis should be monitored carefully for drug resistance and viral breakthrough, as liver enzyme flares may precipitate decompensation events (Koklu et al., 2013). Clinical studies indicate that prolonged and adequate suppression of HBV-DNA with any anti-viral can stabilize liver disease in cirrhotics and prevent decompensation hepatic events (Kim et al., 2012). Regression of liver fibrosis and even reversal of cirrhosis have been reported in patients with prolonged suppression of HBV replication (Chang et al., 2010). Nonetheless, long-term periodic screening for liver cancer is warranted in cirrhotics, who may remain at risk for developing hepatocellular carcinoma.

A second caution relates to primary HBV drug resistance, which may compromise the success of empirically given lamivudine as first-line therapy. Transmission of lamivudine-resistant HBV strains has been reported (Fujisaki et al., 2011; Tuma et al., 2011; Xu et al., 2010), but circulation of these variants is rare in most regions (Baxa et al., 2013). However, if there is strong epidemiological suspicion of infection by a lamivudine-resistant strain, it could be worth performing baseline HBV drug resistance testing before prescribing lamivudine monotherapy.

Our opinions are focused on the more judicious and cost-effective use of anti-virals when HBV-DNA testing is available, but as mentioned above, it is very unlikely that most resource-limited regions will have easy access to HBV-DNA testing. More studies are needed to determine how to better use lamivudine and other anti-viral medications under these circumstances. Guidelines must be developed and tested to determine the best strategy, including the use of inexpensive and freely available serum fibrosis indexes for liver fibrosis assessment, along with aminotransferase levels, platelet counts and the presence or absence of liver disease stigmata. The long-term outcomes of HBV-related morbidity and mortality should also be ascertained in these settings.

Finally, another potential use for lamivudine is as prophylaxis for persons with chronic HBV infection who receive chemotherapy or other immunosuppressive treatment, where the risk of HBV reactivation is as high as 50% and of death due to liver failure is 5–10%. In these patients, the prophylactic use of lamivudine during treatment and for 6–12 months thereafter has been shown to decrease HBV reactivation to 10%, and deaths due to liver failure are very rare (Lok et al., 2012).

In summary, a syllogism may well apply to lamivudine therapy for hepatitis B in the year 2013. The first premise is "*Treatment of HBV-viremic patients is better than no treatment*". The second premise is "*The good should not be against the best*". Therefore "*Chronic hepatitis B-viremic patients should be treated, even when the best anti-virals are not available*". Current scientific evidence indicates that there is still room for lamivudine in hepatitis B therapeutics, if some basic rules are applied. Its wise prescription may provide a unique therapeutic opportunity for a large number of hepatitis B patients worldwide, taking advantage of its uniquely good safety profile, acceptable anti-viral activity, convenient dosing, lack of significant drug–drug interactions and low cost. However, concerns still exist regarding the development of drug resistance, so using lamivudine judiciously is paramount.

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5. Transparency declarations

None to declare.

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