Drugs Treatment of Hepatitis B

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Abstract

Objective: To define the role of those drugs available for hepatitis B treatment and analyze current treatment guides prepared by the leading scientific societies in the field.

Methods: Bibliographic searches were carried out in the databases PubMed and EMBASE, using the search word "hepatitis B," limited by "drug therapy" plus "clinical trial," "meta-analysis," or "guidelines," within the period 1991-2007.

Results: Six drugs are currently available: interferon alfa (conventional or pegylated), lamivudine, adefovir, entecavir, and telbivudine. In normal practice, pegylated interferon has almost completely displaced the conventional variety. HBeAg+ patients with high ALT levels, low HBV DNA counts and genotypes A and B show the best response to interferon.

Lamivudine achieves faster and more potent viral suppression than adefovir; its principal drawback is the resistance that some patients develop. Its role will probably decrease as entecavir and telbivudine become more widespread, as they are associated with less resistance. Adefovir is useful in decompensated patients and/or those resistant to lamivudine.

Because of the response rates it obtains, entecavir could be the drug of choice for HBeAG+ patients, particularly those with higher viral loads. For HBeAg– cases, any drug can be used as a first-choice drug. The main difference between the treatment guides lies in the way they define the illness and the serum markers that indicate active replication: viral loads and HBeAG positivity.

Conclusions: All of the drugs are capable of accomplishing short-term biochemical, viral and histological objectives. There is no unanimous opinion on which patients should be treated with which drugs, during what length of time, and what objectives are to be reached.

Key words: Hepatitis B. Interferon alfa 2b. Pegylated interferon alfa 2a. Lamivudine. Adefovir. Entecavir. Telbivudine. Clinical practice guides.

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Tratamiento farmacológico de la hepatitis B

Objetivo: Definir el papel de los fármacos disponibles para el tratamiento de la hepatitis B y analizar las actuales guías de tratamiento de las principales sociedades científicas relacionadas.

Método: Se realizaron sendas búsquedas bibliográficas en las bases de datos PubMed y EMBASE con el término hepatitis B, limitado a drug therapy y clinical trial, metaanálisis o guidelines, en el período 1991-2007.

Resultados: Actualmente son 6 los fármacos disponibles: interferón alfa (convencional o pegilado), lamivudina, adefovir, entecavir y telbivudina. En la práctica habitual, el interferón pegilado ha desplazado casi completamente al convencional. Los pacientes con antígeno E del virus de la hepatitis B (VHB) positivo (HBeAg+) con concentraciones elevadas de alaninotransferasa (ALT), cifras bajas de ADN-VHB y genotipos A y B son los que mejor responden al interferón. Lamivudina consigue una supresión viral más rápida y potente que adefovir; su principal problema es la resistencia que genera. Probablemente, su papel disminuirá con la incorporación de entecavir y telbivudina, asociados con menores resistencias. Adefovir es útil en los pacientes descompensados y/o resistentes a lamivudina. Debido a las tasas de respuestas obtenidas, entecavir podría ser el fármaco de elección en pacientes HBeAg+, fundamentalmente en los que tienen cargas virales más altas. En HBeAg–, cualquier fármaco podría ser utilizado como primera opción. Las guías difieren, principalmente, en la definición de la enfermedad y los marcadores séricos que indican replicación activa: cargas virales y positividad del HBeAg.

Conclusiones: Todos los fármacos son capaces de alcanzar los objetivos bioquímicos, virales e histológicos a corto plazo. No hay unanimidad acerca de qué pacientes tratar, con qué fármacos, durante cuánto tiempo y cuáles son los objetivos perseguidos.

Palabras clave: Hepatitis B. Interferón alfa 2b. Interferón pegilado alfa 2a. Lamivudina. Adefovir. Entecavir. Telbivudina. Guías de práctica clínica.

INTRODUCTION

Currently, hepatitis B (HBV) viral infection continues to be a serious public health problem worldwide, in spite of recent advances in treatment and prevention of this disease. Currently, there are more than 2 billion people infected with HBV, and almost a fourth exhibit the disease's chronic form. It is also estimated that half a million people die annually due to HBV complications, principally, hepatocarcinoma and liver cirrhosis.[1]

HBV exists worldwide but varies geographically according to prevalence and mechanisms of transmission.

Prevalence is 8% in Africa and Asia, and transmission is mainly perinatal or horizontal. Prevalence is less than 1% in Europe, North America, and Australia, and is most frequently transmitted sexually and parenterally through drug use. Prevalence is approximately 1%-8% in the Mediterranean region. In Spain, almost half of those are infected in adolescence or as an adult where most cases are contracted parenterally, followed by sexual transmission and infection from work in public health.[2,3]

Given its dynamic course, infection can be manifested in various ways; therefore classification is crucial when beginning therapeutic treatment. Clinical cases are usually referenced by phases. First is the immunotolerance phase, characterized by high serum concentrations of HBV-DNA (≥100 000 copies/mL), HBV e Antigen-Positive (HBeAg+), practically normal transaminase values, especially alanine transferase (ALT), and minimal hepatic histological activity. This phase usually lasts longer in newborns or children, but is brief in adolescents and adults. Second is the immunoactivity phase, named for the immunological system's attempts to control infection in the hepatocytes. This is characterized by transaminase elevation and histological activity, and an HBV-DNA decrease. In this phase, seroconversion of HBeAg into antiHBE may occur, this a critical moment in the development of HBV. After seroconversion, ALT normalizes, hepatic inflammation recovers, and HBV-DNA is ≤100 000 cop/mL, becoming an inactive carrier. A percentage of these patients develop mutations in the core or HBV core promoter regions which cause an HBV-DNA elevation, and anti-HBeAg advances to HBeAg+, marking the reactivation phase with necroinflammation.[4]

There are numerous and varied factors which affect the disease's progress. On one hand, there are social, demographic, and environmental factors: age, sex, time of infection, geographic area, and alcohol consumption, and on the other hand, viral factors: genotype, presence of mutations in the core and pre-core regions, viral load, coinfection with other viruses, and positivity or no positivity of the virus' HBeAg.[5-8]

Even though chronic HBV infection has recently become a preventable and treatable disease with treatment advances, the continued low percentage of patients who obtain proper therapy has renewed an interest in this disease.[9-12] Currently, effectiveness continues to be limited, and the risk of presenting with adverse effects is high in spite of available therapeutic options. There continues to be unresolved questions, such as when to treat patients and with what. Nevertheless, scientific societies with various treatment guides have yet to come to an agreement, and furthermore, various authors have proposed different treatment algorithms.

The objective of this review is to clarify and discuss both of these issues and because of these, objectives for this disease and the role of available therapeutic options in our country are determined. Furthermore, the most controversial points on the most relevant clinical practice guides currently available are established.

METHOD

Bibliographic searches were carried out in the biomedical databases PubMed and EMBASE, using the search words *hepatitis B,* limited by *drug therapy* plus *clinical trial, meta-analysis, revisions,* or *guidelines,* between 1991 and 2007. Of the 763 articles collected, only clinical trials on phases II and III published in high impact factor journals were selected. This was a meta-analysis study on hepatitis B drug treatment, and the latest clinical practice guides from the most relevant societies in this area: American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Asociación Española para el Estudio del Hígado (AEEH), and the Asian Pacific Association for the Study of the Liver (APASL), and other treatment algorithms. Likewise, a few additional articles of interest were collected for analysis for answering unresolved questions in previously selected clinical trials. All publications exclusively discussing vaccination or transplants were excluded. Likewise, conference *abstracts* were reviewed from the AASLD and EASL, from 2004 to 2007. Only publications written in English or Spanish were included.

RESULTS

Treatment Objectives and Response Control

Given the infection's characteristics, the objective of treatment may be subdivided into various objectives which should be reached within certain time periods.[13] The first objective should be inhibition of active viral replication, as this is essential for disease manifestation. Other intermediate objectives should then be achieved to increase survival such as decreasing infectivity, suppressing histological activity to avoid the disease's progression, and reducing the risk of cirrhosis and hepatocarcinoma development.[14]

In daily practice, it is not easy to use these final objectives as response criteria, except for patients with decompensated cirrhosis, given the slow evolution of compensated chronic disease. Furthermore, according to the bibliography, elimination of HBV (defined as a loss of HbsAg and subsequent seroconversion into anti-HBs) occurs in less than 10% of patients using drugs currently available.[15] Even when this is achieved, complete viral eradication

is not, with replication persisting due to covalently closed circular DNA copies remaining in the hepatocyte nucleus, which is the type of DNA most resistant to treatment. Only one process of apoptosis of infected cells could achieve real resolution of the infection.

Other definitions of response have been used in various trials developed for assessing efficacy of drugs currently available. Among them is histological response (a decrease ≥2 of necroinflammatory score without Knodell's index of fibrosis score worsening) which is strongly criticized by experts, with its numerous limitations on assessment, such as not allowing early prediction of response to treatments.[16] Therefore, its systematic use is not recommended. The biochemical response is defined as normalization of ALT concentrations, and virological response is defined as the loss of HBeAg with or without seroconversion into anti-HBe or the decrease of HBV-DNA (defined according to different guides as a decrease to values <100 000 cop/mL).[17]

Combined response is defined as the combination of biochemical and virological responses; complete response is defined as a combined response with HBsAg loss (considered infection resolution); these have been tools used recently with the aim of strictly determining usefulness of these drugs to achieve the objectives proposed for this disease.

Efficacy of Available Drugs

Various regulatory agencies (Food and Drug Administration [FDA] and the European Medicines Agency [EMEA]) have approved 6 drugs for chronic HBV infection: interferon alfa 2b (INF-α) and pegylated interferon alfa 2a (PegINF-α), lamivudine (LAM), adefovir (ADF), entecavir (ENT), and telbivudine (LDT). Besides these, other drugs active against HIV, tenofovir (TDF) and emtricitabine (FTC), have shown to be active against HBV, but they currently lack formally approved regimen for this disease (Table 1). Many other new possibilities are in earlier stages of research.

Interferon Alfa 2b and Pegylated Interferon Alfa 2a

Given the theoretical advantages of its administration and the fact that, in daily practice, PegINF-α has almost completely substituted INF-α in general lines of treatment, clinical trials have not completely shown substantial improvement in efficacy results of this formula compared to the traditional one.[18-23]

Treatment efficacy with INF-α and PegINF-α in HbeAg+ patients has been reviewed by various authors[24]; nevertheless, the only current study where efficacy of both interferons has been directly compared was from Cooksley et al[21] (Table 2). In that study, the superiority of PegINF-α over INF-α was determined, based on HBeAg becoming negative along with the decrease or long-term negativization of HBV-DNA and consistent normalization of ALT. Hundred ninety-four patients were included in the study, all were HbeAg+ and randomly selected for receiving INF-α (4.5 MU 3 times per week) or PegINF-α (90, 180, or 270 µg/week). Treatment lasted 24 weeks with a subsequent follow-up period of 24 weeks. Curiously, the best results were obtained from the lowest doses of PegINF-α.

In HBeAg– patients with INF-α, highly varied response rates were found (40%-90%). Nevertheless, the drug's most substantial problem has been the high percentage of patients, around 50%, who relapse after stopping treatment.[25-27] With PegINF-α, Marcellin et al[28] found consistent response rates (including HBV-DNA negativization and transaminases normalizing) of 15% of subjects at 72 weeks, similar to those obtained by one of the comparison groups designed by this study, PegINF-α + lamivudine (LAM), and superior to the group treated with LAM in monotherapy. At 96 weeks, the data from this study has recently been observed, and responses maintain similar values.[29]

In various studies, identification of predictive factors for response to treatment has been attempted with both INF-α[30-32] and PegINF-α. While for HBeAg+ patients, it has been observed that high concentrations of ALT, a low number of HBV-DNA copies, and genotypes A and B best predict a response to treatment, no reliable parameter has yet been described showing the evolution of treatment in HBeAg– patients.[13,24] Nevertheless, it seems that there is a better response for patients with elevated basal concentrations of ALT or those infected by the genotype C.[33]

Lamivudine

The publication of trials on phase III in 2 different populations (Asian and American) established the efficacy of LAM in HBeAg+ patients.[34-36] A histological response was determined in 56% of patients after 52 weeks of treatment. Likewise, seroconversion was achieved in 16% of subjects. With treatment prolonged to 104 weeks,[37] seroconversion of HBeAg was achieved in 27% of cases, and at 3 years in 40%, but the appearance of resistance limited the possibility of more favourable responses. Sustained response, according to the post-treatment follow-up period after seroconversion, was around 38%-77%.[38] Prolonged treatment after seroconversion of HBeAg has demonstrated itself to be favourable if sustained over time.[39]

In studies carried out on HBeAg– patients treated during 48 weeks, undetectable HBV-DNA rates were observed from 68%-73%.[40-43] While normalization of transaminases correlates with decreased viral load, this being accomplished in more than 60% of patients, the percentage of patients with resistance at 1 year was about 18%. Only 1 study, Funk et al,[44] has assessed the response rate sustained by HBeAg– patients after 2 years of treatment. They observed probability of clinical and virological relapse after finishing treatment, of 12% and 30%, 18% and 50%, and 30% and 50% at 6, 12, and 18 months after discontinuing LAM treatment, respectively.

For patients with advanced hepatopathy or established hepatic cirrhosis, the main scientific test for LAM usefulness was provided in the study by Liaw et al[45] carried out on 651 patients with a high degree of fibrosis or cirrhosis, where LAM was compared with a placebo. During an average follow-up period of 32 months,

Table 1. Drugs With an Approved Regimen or Those Accessible as Off-Label for Hepatitis B Treatment in Spain

Ingredient	Interferon Alfa 2b[a]	Interferon Pegylated Alfa 2-a[b]	Lamivudine[c]	Adefovir[d]	Entecavir[e]	Telbivudine[f]	Tenofovir[g]	Emtricitabine[h]
Method of administration	3 MU preloaded syringe	180 µg preloaded syringe	100 mg tablets	10 mg tablets	0.5 mg tablets or 1 mg tablets	600 mg tablets	245 mg tablets	200 mg tablets
Posology cycle	2.5-5.0 MU/m^2 3 times/week, 4-6 months	180 µg/week 48 weeks	100 mg/24 h Undefined	10 mg/24 h Undefined	0.5 mg in treatment-naïve patients and 1 mg in pretreated patients Undefined	600 mg/24 h Undefined	245 mg/24 h Undefined	Undefined
Indications	Treatment of histologically proven chronic hepatitis B, with markers of viral replication, that is positive for HBV-DNA or HBe antigen	Treatment of hepatitis B with positive HBe antigen or negative HBe antigen in adult patients with compensated liver disease and evidence of viral replication, increased ALT, and histologically proven liver inflammation and/or fibrosis	Treatment of chronic hepatitis B in adults with: –Compensated liver disease with evidence of active viral replication, persistently elevated concentrations of alanine aminotransferase, and histological evidence of active liver inflammation and fibrosis –Decompensated liver disease	Treatment of chronic hepatitis B in adults with: –Compensated liver disease with evidence of active viral replication, concentrations of alanine persistently elevated aminotransferase and histological evidence of active liver inflammation and fibrosis –Decompensated liver disease	Treatment of epatitis B chronic infection in adults with compensated liver disease and evidence of active viral replication, concentrations of persistently elevated serum alanine aminotransferase and histological evidence of active inflammation and/or fibrosis	Treatment of chronic hepatitis B in adult patients with compensated liver disease and signs of viral replication, persistently elevated values of serum alanine aminotransferase and histological signs of active inflammation and/or fibrosis	The indication for hepatitis B treatment did not appear at its technical specifications (approval for compassionate use)	The indication for hepatitis B treatment did not appear at its technical specifications (approval for compassionate use)
Advantages	–Limited duration	–Limited duration	–Regimen for decompensated patients –Good tolerance –Low cost	–Regimen for decompensated patients –Less resistance	–Fast response –Less resistance	–High percentage of response	–Less resistance –High effectiveness –Useful in coinfected patients	–Useful in coinfected patients –Good safety profile
Disadvantages	–Subcutaneous administration –Poor tolerance –High cost –Not in decompensated patients	–Subcutaneous administration –Poor tolerance –High cost –Not in decompensated patients	–High rate of resistances (70% at 5 years)	–Related to renal toxicity	–Decreased sensitivity in patients resistant to lamivudine	–Insufficient experience –High resistance	–No approved regimen –Adverse renal effects	–No approved regimen –Similar to lamivudine, possibility of resistance

Table 2. Summary of Results from the Cooksley et al[21] Study of HbeAg+ Patients Treated With Interferon

	INF-α 4.5 M/3 Times/Week	PegINF-α 90 µg/Week	PegINF-α 180 µg/Week	PegINF-α 270 µg/Week
Loss of HBeAg	25%	37%	35%	29%
Seroconversion	25%	37%	33%	27%
Undetectable HBV-DNA[a]	25%	43%	39%	27%
ALT normalization	25%	43%	35%	31%
Combined response[b]	12%	27%	28%	19%

[a]Considered less than 500 copies/mL.
[b]HBeAg negative+ indetectable HBV-DNA + ALT normalization.
Taken from: Cooksley et al.[21]

7.8% of patients treated with LAM achieved the primary objective of clinical progression, compared with 17.7% with placebo. Forty-nine percent developed YMDD mutations, with less clinical benefit compared to those who stayed on LAM with no resistance appearing. Papatheodoridis et al[46] observed the same clinical benefit in a retrospective study with anti-HBe+ patients and proved that early initiation of ADF treatment for patients resistant to LAM reduced the risk of complications compared to patients who had never been treated or who did not respond to interferon.

Pre-treatment ALT values seem to be the most useful factor for predicting seroconversion during LAM treatment. As with interferon, patients with normal ALT values do not seem to benefit from LAM treatment.[47,48]

Unfortunately, LAM has a high rate of resistance, appearing in an average of 15%-20% of patients/year. Its evolution is associated with a loss of clinical response, ALT elevation, and worsening of hepatic histology. Because of this, long-term results from LAM treatment are rare, especially from the HBeAg+ population.[49,50]

Adefovir

The efficacy of ADF in HBeAg+ patients has been evaluated in numerous studies.[51] However, one with possibly the most relevance is the Marcellin et al trial,[52] carried out on 515 randomly selected patients who received a dose of 10 or 30 mg, or placebo, with assessment of histological improvement being the main objective. Secondary objectives were assessment of virological and biochemical response, and the proportion of patients with HBeAg seroconversion. At 48 weeks of treatment, histological improvement was achieved in 55% and 59% of patients who took ADF in 10 and 30 mg dosages, and in 25% of the placebo group. HBV-DNA became undetectable in 21% and 39% of patients, respectively, and ALT normalization occurred in 48% and 55% of those treated with 10 and 30 mg, respectively. Loss of HBeAg was determined in 24% and 27% of patients treated with ADF, and 12% and 14% developed anti-HBe. Of the patients from this study, 309, 296, 231, and 84 continued treatment in a new open-label and non-controlled study, all with a 10 mg dosage, responses evaluated at 48, 96, and 144 weeks, respectively. HBV-DNA became undetectable in 28% at one year and up to 45% and 56% in the second and third years, respectively. Normalization of serum ALT values occurred in 58%, 71%, and 81%, respectively. HBeAg loss occurred in 21%, 42%, and 51% of patients after the first, second, and third year; with anti-HBe seroconversion in 12%, 29%, and 43% after 1, 2, and 3 years of treatment, respectively.[53]

In HBeAg– patients, ADF also proved to be useful according to the Hadziyannis et al trial,[54] compared with a placebo, carried out in 185 patients treated during 48 weeks, where the primary objective was also histological response. At 48 weeks, 64% in the ADF group achieved histological improvement compared with 33% from the placebo group ($P<.001$). Likewise, 51% of patients treated with ADF achieved undetectable HBV-DNA figures compared with 0% from the placebo ($P<.001$). ALT concentrations normalized in 72% and 29% in the ADF and placebo groups, respectively. When ADF treatment was interrupted at 48 weeks, patients were re-assigned with ADF or a placebo, in a second study with an open-label design. Patients who had initially received a placebo were assigned ADF 10 mg/day. At 96 weeks, those who received ADF were advised to continue on ADF. Viral load was less than 1000 copies/mL for 71% of patients who received ADF. On the contrary, a benefit loss was already observed at the fourth week in the majority of patients who changed from ADF to placebo, and only 8% had <1000 copies/mL at week 96. The decrease of transaminases was significantly greater in the groups which continued with ADF or changed from placebo to ADF than in the group which changed from ADF to placebo ($P=.01$), and in week 96, 73% and 80% of groups receiving ADF had a normal ALT value compared to 32% of the placebo group. ALT remained the same in the group continuing to week 144, with normalization in 69% of those patients.[55,56]

ADF has been evaluated in various studies for patients resistant to LAM. The Kim et al[57] study was carried out on 46 subjects with decompensated hepatopathy, HBeAg+, and HBV resistant to LAM; patients were treated with ADF or LAM + ADF for 24 weeks. Eighty-three percent of patients from the monotherapy group, and 86% from the combined therapy group achieved undetectable concentrations of HBV-DNA. Transaminases normalized in 78% and 82% of patients. Peters et al[58] selected patients with compensated liver disease, HBeAg+ with a genotype resistant to LAM, elevated ALT concentrations, and HBV-DNA >1 000 000 copies/mL, and they were randomly selected to

receive ADF, LAM, or LAM + ADF. The primary objective was HBV-DNA decrease at 16 weeks. HBV-DNA decreased –0.07 $\log_{10}$ in the LAM group and was greater, but similar, between the ADF and ADF + LAM groups (–2.45 $\log_{10}$ and –2.46 $\log_{10}$ copies/mL; *P*<.001). At 48 weeks, the HBV-DNA decrease was 0.0 $\log_{10}$; –3.59 $\log_{10}$ and –4.04 $\log_{10}$ copies/mL.

In the Perrillo et al[59] placebo controlled study, the efficacy and safety of ADF addition to 135 patients with YMDD mutation were evaluated. Of the 95 patients with compensated hepatitis (group A), 46 were assigned with ADF treatment and 49 with placebo during 52 weeks, while continuing with LAM; the remaining 40 patients with decompensated cirrhosis or post-transplant hepatitis B, were assigned with ADF + LAM (group B). The principal objective was DNA frequency decrease to 100 000 copies/mL or a reduction of 2 $\log_{10}$ copies/mL based on basal determination, at 48 and 52 weeks of treatment. HBV-DNA decreased in 85% of patients from combined treatment group A and decreased in 24% of those receiving LAM (*P*<.001). In group B, 92% had virological response and biochemical improvement (*P*<.001). Lastly, the Schiff et al[60] study carried out in 324 LAM resistant patients, applying to both pre and post-transplant conditions, demonstrated that the addition of ADF improves survival of these patients at 1 year (84% were pre-transplant and 93% post-transplant), and achieves a good degree of response regarding virological, biochemical, and histological objectives.

Until now, sufficiently reliable predictive factors for response, which can predict subgroups of patients with a high initial probability of responding to ADF, have not been described.[61,62]

Onset of ADF resistance has been described as slow. N236T and A181V mutations have been related to decreased sensitivity of ADF, but with emtricitabine and LAM treatment for the first mentioned, and tenofovir for the second, there is possibility for a resolution. The percentage of resistances appearing in patients treated with ADF is annually accumulative at 2.5% for the first 4 years of treatment.[63]

Entecavir

In a pivotal clinical trial carried out on HBeAg+ patients, 715 subjects with compensated liver disease were randomly selected to receive ETV or LAM.[64,65] At 48 weeks, histological response rates of 72% and 62% were obtained from groups treated with ETV and LAM, respectively. Virological response rates (HBV-DNA <0.7 mEq/mL) were 67% and 36%, and biochemistries (normalization of transaminases) were 68% and 60% in each group. At 48 weeks, complete response (defined as the sum of virological response + e antigen negative) was 21% for the ETV group compared with 19% for the LAM group.

In a study designed for HBeAg– subjects, a total of 648 patients were included.[66] The study's main objective was improvement of anatomopathological lesions, and this was observed at week 48 of treatment in 70% of patients from the ETV group and in 61% from the LAM group. These differences were statistically significant, along with virological parameters (percentage of patients with negative viral DNA, 90% compared with 72%), and biochemical parameters (normalization of transaminases, 78% compared with 71%), for patients from the ETV and LAM groups, respectively. Percentages of complete response (virological response + e antigen negative) were 85% and 78%, respectively.

ETV has also been studied in patients previously treated with LAM.[67-69] Specifically, in the Tassopoulos et al study,[68] 181 patients resistant to LAM were randomly selected to receive 3 different dosages of ETV (0.1, 0.5, and 1 mg daily) or 100 mg of LAM. After 24 weeks of treatment, the percentage of patients with undetectable HBV-DNA was at 19% in the 0.1 mg ETV group, 53% in the 0.5 mg ETV group, 79% in the 1 mg ETV group, and 13% in the LAM group (*P*<.0001). More recently, Sherman et al[69] published another trial on phase III for determining efficacy and safety of ETV compared with LAM in patients resistant to LAM. 240 patients were included who were only HBeAg+. The percentages of patients with histological improvement (55% compared with 28%), and virological response (19% compared with 1%) and biochemistry (61% compared with 15%) were significantly better in the ETV group. This was not the case with the percentage of seroconversion (8% compared with 3%).

Predictive factors for response to ETV have still not been determined, as this drug seems to be equally effective in patients of different races, as with various HBV genotypes, and with a broad interval of ALT concentrations increase.[70,71]

ETV resistance rates were described at only 3% in treatment-naïve patients at 96 weeks of treatment; these rates were related to previous resistance to LAM.[72,73]

Telbivudine

LDT efficacy has been proven in GLOBE 007 pivotal studies[74] carried out on 1367 patients between HBeAg+ and HBeAg–, compared to LAM. The majority of patients in these studies were Asian. The main variable was response to therapy and was defined as the combination of virological response + serum HBeAg loss or ALT normalization.

In HBeAg+ patients (n=921), LDT was superior to LAM in terms of therapeutic response (75.3% compared with 67.0%; *P*=.0047). However, for HBeAg– patients (n=446) it only showed it was not inferior to LAM (75.2% compared with 77.2%; *P*=.6187). In Table 3, other virological, biochemical, and serological variables collected at 52 weeks of treatment are shown.[75]

Caucasians were associated with an inferior response in both treatment groups; however, the population of Caucasian patients included was the minority (n=98) with respect to the total.

Recently, Chan et al[76] compared LDT and ADF in an open-label study with treatment-naïve HBeAg+ patients. Patients were randomly selected to receive LDT, ADF, or ADF during the first 24 weeks and LDT for the remaining 28, until completing a year of treatment. LDT showed a greater and more consistent decrease of HBV-DNA after 24 weeks of treatment, and at a year of

treatment, HBV-DNA decrease was greater in the group of patients with continued LDT treatment than in ADF-LDT alternative groups (at week 52, average values of HBV-DNA were at 3.01 $\log_{10}$ copies/mL [LDT group] and 3.02 $\log_{10}$ copies/mL [ADF-LDT group] compared with 4.00 $\log_{10}$ cop/mL [ADF group]).

The special mechanism of action of LDT theoretically would make the appearance of resistant mutations difficult, because it acts as a synthesis inhibitor of the second strand of viral DNA. Nevertheless, resistance rates of 21% were described for patients treated for 2 years with the drug.[77-80]

Drugs in Development

Tenofovir

In the broadest current study published for assessing TDF[81] usefulness in treating HBV in coinfected patients, Benhamou et al[82] showed the drug's efficacy combined with LAM for treating both HBeAg+ and HBeAg– subjects; it is worth noting that the majority of the 65 patients included in this retrospective study showed YMDD mutation associated with LAM resistance. After 48 weeks of TDF treatment, HBV-DNA reductions were determined at 4.56 $\log_{10}$ copies/mL for HBeAg+ and 2.53 $\log_{10}$ copies/mL for HBeAg–. The percentage of patients with undetectable viral load was 29.6% and 81.6% for HBeAg+ and HBeAg–, respectively. A duration of virological response of 100% and 66.6% was collected from HBeAg+ y HBeAg– subjects, respectively.

Likewise, TDF has shown to be superior in small comparative studies with other drugs active against HBV,[83-85] such as ADF in patients previously resistant to LAM, with both coinfected and monoinfected patients.[86-88] In the van Bommel et al[86] study, 100% of patients achieved HBV-DNA concentrations <100 000 copies/mL compared with 44% of those treated with ADF, without noticeable adverse effects or resistance appearing.

Until now, no cases of reactivation of HBV infection as a consequence of TDF resistance have been published, but more prospective studies continue to be necessary which assess the drug's long-term efficacy, duration of HBV-DNA suppression, seroconversion rates, and potential resistance, such as long-term safety when combined with other drugs such as LAM or FTC.[89] Various phase III clinical trials are currently in process, where the usefulness of TDF in different types of patients and comparison with various controls is evaluated (Table 4).

Currently, only Jain et al[90] have indicated that genotype A patients with HBV infection respond best to TDF treatment.

Given the fact that TDF has shown strong activity against HIV and promising efficacy in studies carried out on HBV patients, both monoinfected and coinfected patients have made it where TDF is the current drug of choice for HBV/HIV coinfection treatment, especially in patients with less than 350 cells/μL CD4.[91-93]

Emtricitabine

In the Lim et al study[94,95] carried out on monoinfected HBV patients, FTC was compared with a placebo; at 48 weeks of treatment, 54% of patients achieved undetectable HBV/DNA (39% HbeAg+ and 79% HbeAg–), 65% had transaminase normalization, and 12% had seroconversion. On the contrary, 13% of patients had developed mutations at the end of the study which caused resistance to the drug.

The combination with TDF has also been useful for patients with failed ADF treatment.[96] On the other hand, the addition of clevudine to FTC treatment does not seem to increase treatment efficacy.[97]

Clevudine

To date, the study of most interest carried out on HBeAg+ patients was Yoo et al[98] where 243 Asian patients were compared between 30 mg clevudine and a placebo for 24 weeks of treatment. The drug was well tolerated and showed a marked decrease of viremia (–5.1 compared with –0.2 $\log_{10}$). Transaminases normalized in 68% compared with 17% of groups at the end of the study and maintained a similar proportion for the 24 week follow-up period.

In a similar study carried out on 86 HBeAg– patients,[99] a marked decrease of viremia was observed which continued after stopping treatment. At 24 weeks after treatment interruption, 70% of patients presented with normal transaminase values.

Although clevudine resistance has still not been well defined, in clinical studies a few mutations have been observed in the polymerase region, a reason why there are signs of possible cross-resistance with LAM.

Table 3. Virological, Biochemical, and Serological Variables in Telbivudine Pivotal Studies

	HBeAg+ (n=921)		HBeAg– (n=446)	
Variable	**Telbivudine (n=458)**	**Lamivudine (n=463)**	**Telbivudine (n=222)**	**Lamivudine (n=224)**
HBV-DNA reduction[a]	–6.45	–5.54	–5.23	–4.4
ALT normalization	77%	75%	74%	79%
HBeAg seroconversion	23%	22%	–	–
HBeAg loss	26%	23%	–	–
Histological improvement	71%	61%	71%	70%

[a]log copies/mL, average value.
Taken from EPAR,[75] Chan HL et al,[76] and Lai CL et al.[77]

Table 4. Clinical Trials in Process for New Drugs in Hepatitis B Treatment[a]

Drug	Control	Title of Study	Phase	Number of Patients	Start Date	Promoter
Tenofovir	Emtricitabine/ tenofovir	A randomized, double-blind study evaluating tenofovir disoproxil fumarate monotherapy versus the combination of emtricitabine and tenofovir DF for the treatment of chronic hepatitis B	II	100	August 2007	Gilead
Tenofovir	Emtricitabine/ tenofovir Entecavir	Phase II, double-blind, multicenter, randomized study comparing tenofovir disoproxil fumarate, emtricitabine/tenofovir, and entecavir in the treatment of chronic hepatitis b subjects with decompensated liver disease and in the prevention of hepatitis B recurrence post-transplantation	II	100	March 2006	Gilead
Tenofovir		Tenofovir disoproxil fumarate alone versus its combination with emtricitabine for treatment of chronic hepatitis B	II	100	August 2007	National Institute of Diabetes and Digestive and Kidney Diseases
Tenofovir	Pegylated interferon Emtricitabine/ tenofovir	Pegylated Interferon Alfa-2a Versus Emtricitabine/Tenofovir ± Pegylated Interferon Alfa-2a for the Treatment of Chronic HBe-Ag Positive Hepatitis B Infection in HIV-Coinfected Patients - the PEGPLUS Trial	III	72	September 2004	Hoffmann-La Roche
Tenofovir	Emtricitabine/ tenofovir + Immunoglobulin antihepatitis B Emtricitabine/ tenofovir	Phase 2, Open-Label Randomized Study to Evaluate the Efficacy and Safety of the Combination Product, Emtricitabine/Tenofovir Disoproxil Fumarate in the Presence or Absence of Hepatitis B Immunoglobulin (HBIG) in Preventing Recurrence of Chronic Hepatitis B (CHB) Post-Orthotopic Liver Transplant (OLT)	II	50	August 2007	Gilead
Tenofovir	Entecavir	A Comparative Study of Chronic Hepatitis B Subjects Treated With Entecavir Plus Tenofovir Combination Therapy Versus Entecavir Monotherapy in Adults Who Are Treatment-Naïve to Nucleosides and Nucleotides: The BE-LOW Study	III	384	April 2007	Bristol-Myers Squibb
Tenofovir	Emtricitabine/ tenofovir Pegylated interferon	Pilot Study on Efficacy and Tolerance of Peg-Interferon Alfa-2a (Pegasys) Added to Tenofovir DF and Emtricitabine (Truvada) in AGHBe Positive HBV-HIV co-Infected Patients	III	55	March 2007	French National Agency for Research on AIDS and Viral Hepatitis
Emtricitabine		Virological and Clinical Anti-HBV Efficacy of Tenofovir and Emtricitabine in Antiretroviral Naive Patients With HIV/HBV co-Infection	II	24	April 2005	HIV Netherlands Australia Thailand Research Collaboration
Clevudine		Phase IV Study to Evaluate the Safety and Efficacy of Clevudine Compared With Clevudine and Vaccine in Patients Chronically Infected With HBV, HBeAg(+)	IV	70	May 2007	Bukwang Pharmaceutical
Clevudine	Lamivudine	A Phase II, Double-Blinded, Randomized Study to Compare the Efficacy and Safety of 48-Week Treatment With Clevudine 30 mg qd Versus Lamivudine 100 mg qd for Chronic Hepatitis B Infection	II	92	June 2007	Bukwang Pharmaceutical
Clevudine	Adefovir	A Multi-Center, Randomized, Double-Blind, Active-Control, 96 Week, Phase III Trial of the Efficacy and Safety of Clevudine Compared With Adefovir at Weeks 48 and 96 in Nucleoside Treatment-Naïve Patients With HBeAg Negative Chronic Hepatitis Due to Hepatitis B Virus	III	?	August 2007	Pharmasset

(Continued)

Table 4. Clinical Trials in Process for New Drugs in Hepatitis B Treatment[a] *(Continuation)*

Drug	Control	Title of Study	Phase	Number of Patients	Start Date	Promoter
Valtorcitabine	Telbivudine	Randomized, Blinded, Phase IIb Trial of Telbivudine (LdT) Versus the Combination of Telbivudine and Valtorcitabine (Val-LdC) in Patients With Chronic Hepatitis B	II	Study in process not recruiting patients		Novartis
Pradefovir	Adefovir	Dose-Ranging Study of Pradefovir in Patients With Compensated Hepatitis B	II	Not in selection		Valeant Pharmaceuticals North America
Pradefovir	Adefovir	Open-Label Treatment Extension Study for Patients Who Complete Study RNA200103-201	II	Not in selection		Valeant Pharmaceuticals North America

The RNA200103-201 study is titled: Dose ranking study of pradefovir in patients with compensated hepatitis B.
[a]Table by this author based on the reference.
Taken from Clinical Trials.[119]

Valtorcitabine

In a 4 week dose-ranging study on HbeAg+ patients, efficacy of various dosages of valtorcitabine (50, 100, 200, 300, 600, 900, and 1200 mg/day) administered orally in distinct daily doses was evaluated. At the end of the treatment period, all groups were able to reduce HBV-DNA concentrations. Notably, patients with the highest dosages experienced an inferior viremia decrease than what was observed with the 900 mg[100] dosage.

Until now, no resistance to valtorcitabine has been described, but this may appear, because it shares mutations which cause resistance to lamivudine. Valtorcitabine was designed in its development for combined administration with telbivudine.

Pradefovir

At 24 weeks after beginning of treatment, preliminary results from a trial presented in the AASLD conference demonstrated better response rates of viral load decrease for 3 out of 4 treatment groups taking pradefovir compared with a group of patients with ADF as the control drug. Nephrotoxicity problems were not observed in any groups. The majority were HbeAg+ patients (70%) and had been pretreated beforehand.[101]

Other Drugs

Another drug projected for HBV treatment but with fewer scientific tests is, among others, racivir, a polymerase inhibitor of HBV-DNA, currently in studies on phase II. Structurally it is very similar to LAM and FTC, because based on observation, it is active against both HBV and HIV. Nitazoxanide is a drug used for intestinal parasitosis treatment in children and could also be useful against HBV and hepatitis C. NOV-205 is an immunomodulator agent which acts as a hepatoprotector, with antiinflammatory properties. It is currently approved in Russia for hepatitis C and HBV (Molixan®) treatment, but in Europe, its legal status is unknown. EHT899 is a viral protein administered orally, designed to eliminate undesirable immune response induced by HBV. In an initial trial carried out on 42 patients with HBV treatment during 48 weeks, 46% achieved HBV-DNA decrease, and 33% decreased inflammation analyzed through biopsy.[102]

Clinical Practice Guidelines

Currently, there is no universally accepted criterion on which patients to treat and with what drugs. The most consolidated treatment guides such as AASLD, EASL, AEEH, and APASL differ regarding the transaminase threshold (at least 2 times above the upper normal limit) and serum markers (elevated concentrations of DNA and positive HBeAg)[103-106] (Table 5).

All of these recommendations have been highly criticized by various subject experts.[107-111] Among the most debated issues is the fact that, on one hand, many patients with ALT concentrations, who do not reach the value of 2 times above the upper normal limit or who even show normal ALT values, may present with liver disease, as there are enough scientific tests which indicate that ALT concentrations do not correlate with the degree of fibrosis. In the Yang et al study,[112] it was demonstrated that more than 45% of patients with HBV infection and normal ALT concentrations are in stage 2 fibrosis or higher. Iloeje et al[113] observed that ALT concentrations do not strongly predict the development of hepatocarcinoma, cirrhosis, or death. With this, it is believed that although ALT concentrations allow for identification of patients with active disease,[114,115] they may also

cause some patients with significant inflammation to be missed in diagnosis.[110] On the other hand, also criticized has been the fact that a HBV-DNA concentration of 10^5 copies/mL, indicated as a decisive point for treating or not treating,[16] could prove to be too elevated, principally in HBeAg– subjects with mutation in the pre-core region.[112,116,117]

The most updated AASLD guidelines[103] recommend always treating HbeAg+ patients who present with values >100 000 cop/mL of HBV-DNA and ALT values 2 times above the upper normal limit, or if this parameter is normal, when the biopsy shows moderate/serious inflammation or significant fibrosis. HBeAg– patients who present with values >100 000 copies/mL of HBV-DNA and ALT 2 times above the upper normal limit should be treated. Likewise, those who present with numbers between 10 000 and 100 000 copies/mL should begin treatment and always when their numbers surpass double the normal limit for ALT and when liver biopsy shows moderate-serious inflammation or significant fibrosis appears. Until now, the consensus guideline which recommended treatment with lower HBV-DNA values was Spanish. This only requires values >10 000 copies/mL and transaminase elevation. The remaining documents, EASL,[104] APASL,[105] and algorithms proposed by other authors such as Keeffe,[107,108] maintain that treatment should begin with values >100 000 copies/mL (Table 5).

Regarding the other major question of what drug to use, the selection of one therapeutic option in detriment of the others as first line treatment becomes complicated due to, on one hand, the absence of comparative studies, and on the other, primary objectives of clinical trials have not been uniform, nor have definitions of response and methodology used for quantifying viral replication or for detecting resistance.

It is necessary to take into account that a significant number of patients will achieve seroconversion independently from the treatment used. The difference lies in duration of treatment, 6-12 months for INF-α or PegINF-α, and 1-4 years or more for nucleoside/nucleotide analogues.

HBeAg+ patients with elevated ALT values and low viral load who are treated with PegINF-α are those who best respond to treatment; nevertheless, these characteristics also allow identification of patients who best respond to nucleoside analogues. Moreover, the idea has been spread that seroconversion induced by PegINF-α lasts longer than that by LAM or ADF after a year of treatment; however, it is difficult to maintain this assertion, considering that none of these nucleoside analogues is used this way in clinical practice. Therefore, it is logical to think that maintaining seroconversion with nucleoside analogue drugs after more than a year of treatment could be superior. Researchers who indicate that HBAg loss is greater with PegINF-α than with the rest of the analogues maintain similar affirmations.[110] If the data are compared not for 1 year but for up to 4 years, rates may be even greater for drugs such as ADF and LAM, and we are yet to know if this will also be so with ETV and LDT.

In any respect, around 30%-40% of patients will achieve seroconversion, while 60%-70% will need other treatments. Here it is of crucial importance to minimize the appearance of resistance.

Ideally, all patients should achieve figures of HBV-DNA <10 000 copies/mL (Tables 6 and 7). In this respect, even though LAM has shown a faster and stronger suppression than ADV, its main problem is the elevated rate of resistance it generates, a reason why its role in hepatitis B treatment is hoped to decrease in the future, with ETV and LDT becoming incorporated, which are associated with a lower rate of resistance. The rates of complete responses obtained indicate that ETV could be the drug of choice for HBe-Ag+ patients, especially for those with higher HBV-DNA figures (Table 8). For HBeAg– and compensated disease treatment, where carrying out a thorough and repeated assessment of viral replication is essential, INF-α or PegINF-α, LAM, ADF, ETV, and LDT could be used as a first line of treatment. However, the fact that the consistent response is rarely reached in these patients and that treatments are needed over a very long time period to maintain suppression of viral replication could lead to consideration that, based on currently available data on complete

Table 5. Assessment of Treatment Initiation According to Different Clinical Practice Guidelines for Hepatitis B Treatment

	HBeAg+		HBeAg–	
	DNA HBV	**ALT**	**DNA HBV**	**ALT**
EASL 2003	>100 000	>2 x AUNL	>100 000	>2 x AUNL
APASL 2005	>100 000	>2 x AUNL	>100 000	>2 x AUNL
AEEH 2006	>10 000	Elevated	>10 000	Elevated
AASLD 2007	>20 000 U/mL	>2 x AUNL	>20 000 U/mL	>2 x AUNL
	>20 000 U/mL	≤2 x AUNL and biopsy[b]	>2000 U/ml	1-2 x AUNL and biopsy[b]
Keeffe 2004 and 2006	<100 000	Normal if lesion[a]	<100 000	Normal if lesion[a]
	≥100 000	Normal if lesion	≥10 000	Normal if lesion
	≥100 000	Elevated	≥100 000	Elevated

1 U/mL = 5 copies/mL.
[a]Significant.
[b]Moderate/serious inflammation or significant fibrosis.
Taken from: EASL Jury,[104] Liaw et al,[105] Consensus Document AEEH,[106] Keefe et al.[107,108] and Hoofnagle et al.[109]

responses and with more data expected on subgroups of particular patients, subjects with lower HBV-DNA values could benefit from treatment with PegINF-α, LAM, or ADF, and those with higher HBV-DNA values, from ETV or LDT treatment.

Recently, Keeffe et al[118] drew up the "routing sheet" for using drugs orally in hepatitis B treatment. The given protocol recommends intensive control of serum HBV-DNA for identifying treatment results, at both 12 and 24 weeks after beginning treatment and assesses responses as complete, partial, or inadequate, based on the speed of viral load suppression, and therefore, it seeks to decrease the appearance of mutations which cause resistance to the drugs. Although the given document is quite promising for maximizing efficiency of various treatments available, it should still be validated by future prospective studies testing its effects.

For compensated cirrhosis, including both HBeAg+ and HBeAg–, ADF currently seems to be the best therapeutic option, and for decompensated cirrhosis, including both types of patients, LAM combined with ADF seems to achieve best results.

DISCUSSION

Today, chronic hepatitis B treatment continues to be a first order health challenge, and in spite of recently broadened therapeutic possibilities, therapeutic results still continue to be limited.

Likewise, it is difficult to establish universal recommendations of which patients are treated, with what drugs, and for how much time. In this lie the very characteristics of the virus, that even though patients may achieve response, there is still no eradication. This has caused an absence of appropriate response criteria which accurately reflect clinical evolution, and because of this, in recent years, different response criteria have been used in clinical trials developing various drugs and has made their comparison difficult.

In general lines of treatment, the tendency should be to combine the greatest percentages of responses with the least time of treatment, minimizing adverse effects. Additionally, based on the fact that the overall majority of patients will need more than one treatment drug, they should be prescribed one where, if resistance appears, another could be opted for a rescue alternative.

Regarding this, in spite of its posological advantages, PegINF-α offers results for HBeAg+ patients with

HbeAg negativization, which are very similar to those obtained previously with conventional INF-α, with the difference that PegINF-α was used for 48-52 weeks, while, in general, conventional IFN-α was normally used for half that time. Furthermore, the addition of LAM to PegINF-α treatment does not seem to increase efficacy.

Comfortable administration, fast and strong inhibition of viral replication, and a good safety profile made LAM combined with INF-α the first drug of choice for years. Nevertheless, the appearance and presupposition of resistant mutants counteract their good clinical profile. Because of this, it is hoped that in the near future, it loses prominence to new drugs with equal or greater antiviral activity but with less development of resistance.

Table 6. Documented Genetic Resistances to Available Drugs for Treatment of HBV Chronic Infection

Drug/ Mutation	Lamivudine/ L180M + M204V	Adefovir/ N236T	Adefovir/ A181V
Drugs with cross-resistance (not selected)	Clevudine Emtricitabine Entecavir Telbivudine	Clevudine Tenofovir	Entecavir Lamivudine
Drugs without cross-resistance (selected)	Adefovir Lamivudine	Emtricitabine Tenofovir	Tenofovir

Taken from Fraga et al.[61]

Table 7. Comparative Data on Documented Resistances Based on Duration of Treatment for Some of the Drugs Available for Treating Chronic HBV Infection

	1 Year	2 Years	3 Years	4 Years	5 Years
Lamivudine	24%	38%	53%	66%	69%
Adefovir	0%	3%	11%	18%	29%
	11%[a]	34%[a]			
Entecavir	0%	0%	1%	–	–
	6%[a]	8%[a]			
Telbivudine		21%	–	–	–

[a]For patients resistant to lamivudine. Modified from Cardenas M. (Entecavir Report, for Andalusian Pharmacotherapeutic Reference Guidelines).
Taken from EPAR Report.[34,51,64,75]

In this line, ADF continues to be a highly useful drug, both in treatment-naïve patients as in LAM resistant ones. It could continue to be a first-choice drug for these types of patients because of its breadth of uses and effectiveness shown in cirrhotic and decompensated patients.

Currently, ETV has achieved the greatest percentage of complete responses among all available drugs. Also, development of resistance has been infrequent until now and only appears in subjects with previous LAM resistance. All of this makes it a preferred drug for treatment-naïve patients, principally for HBeAg+ patients.

Even though studies have shown the LDT superiority over LAM for HBeAg+ treatment and no inferiority for HBeAg– treatment, its usefulness is yet to be established for patients previously resistant to LAM. Likewise, its main a priori weak point is the high percentage of resistance it presupposes, even higher than ADF. Maybe in a direct comparative study with ENT, it could be established whether LDT should be regarded as a first line of treatment.

In spite of good expectations generated from new possibilities in development, it is still early to identify the actual role these will play in the near future.[119,120] Otherwise, it is fitting to think

Table 8. Comparative Results Obtained From Various Available Drugs for Hepatitis B, Measured at 1 Year of Treatment

Type of Patient	Pegylated Interferon[a]	Lamivudine[b]	Adefovir[c]	Entecavir[d]	Telbivudine[e]
Virological response					
HBeAg+	25%	39%	21%	67%	60%
HBeAg–	63%	72%	51%	90%	88%
ALT normalization					
HBeAg+	39%	66%	48%	68%	77%
HBeAg–	38%	74%	72%	78%	74%
Histological improvement					
HBeAg+	38%	59%	53%	72%	65%
HBeAg–	48%	63%	64%	70%	66%
HBeAg loss (HBeAg+) or HBsAg loss (HBeAg–)					
HBeAg+	30%	22%	24%	22%	26%
HBeAg–	4%	<1%	<1%	<1%	<1%

[a]Lau et al,[23] Hui et al,[24] and Marcellin et al.[29]
[b]Lai et al[35] and Dienstag et al.[36]
[c]Marcellin et al[52] and Hadziyannis et al.[55]
[d]Chant et al[65] and Lai et al.[66]
[e]Informe EPAR[75] and Lai et al.[77]

that, as with other infectious diseases such as HIV or hepatitis C, the most suitable treatment could consist of drug combinations with different mechanisms of antiviral action, easy administration, and good safety profiles. In this line, the possibility that TDF will replace ADF for HBV treatment will depend on confirmation of its efficacy in terms of superior virological response and comparable safety, especially and fundamentally for renal toxicity, its efficacy against wild and mutant strains (such as those which express YMDD which cause resistance to LAM, EMT, LDT, or clevudine), and a low rate of resistance, both in treatment-naïve and pretreated patients.

In conclusion, in spite of good short-term results obtained from currently available drugs, we continue to wait for unanimity to be achieved regarding the selection of patients for treatment and the definition of sought after responses. In awaiting unanimity, the best answer to these concerns may be to carry out a detailed selection, both of patients receiving treatment and of available drugs, and pay attention to peculiarities of each individual case.

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