CURRENT TREND

Analogs and fibrosis regression in hepatitis B

Analogues et régression de la fibrose dans l’hépatite B

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Summary  Nucleoside or nucleotide analogs (NUCs) are a major step forward in the treatment of hepatitis B virus (HBV) infection. Apart from their proven antiviral efficacy, these drugs have proved able to significantly improve liver fibrosis as short-term treatment. Using different definitions of fibrosis regression, after 1 year of treatment, improvement in liver fibrosis was observed among HBe antigen (HBeAg)-positive naive patients: 35—61% with lamivudine; 41% with adefovir; 68% with telbivudine; 39% with entecavir; and 74% with tenofovir. Among HBeAg-negative patients, after 1 year of treatment, improvement in liver fibrosis was seen in: 36—46% with lamivudine; 48% with adefovir; 56% with telbivudine; 36% with entecavir; and 71% with tenofovir. Long-term treatment is often required with NUCs; the response continue to improve over time, reaching up to 63% of patients with lamivudine and 71% of patients with adefovir, although the development of antiviral drug resistance can blunt any histological improvement. Also, there is now growing evidence that non-invasive methods of fibrosis diagnosis, such as surrogate markers, are likely to become as important as liver biopsy for taking the initial decision to biopsy and for treatment, and in the follow-up of treated chronic HBV patients.

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Résumé  Les analogues nucléosidiques ou nucléotidiques sont un progrès majeur dans le traitement des hépatites chroniques B. En dehors de leur efficacité antivirale prouvée, ces molécules ont montré une amélioration significative de la fibrose chez les patients traités. En utilisant des définitions différentes de régression de la fibrose, un traitement d’un an entraîne une amélioration de la fibrose chez les patients antigène HBe positif naïfs de traitement chez 35 à 61 % des patients traités par lamivudine, 41 % des patients traités par adéfovir, 68 % des patients traités par telbivudine, 39 % des patients traités par entécarvir et 74 % des patients traités par ténofovir. Chez les patients antigène HBe négatif, à un an, une régression de la fibrose est observée chez 36 à 46 % des patients traités par lamivudine, 48 % des patients traités par adéfovir, 56 % des patients traités par telbivudine, 36 % des patients traités par entécarvir et 71 % des patients traités par ténofovir. Un traitement prolongé est très souvent nécessaire avec les analogues et l’amélioration de la fibrose se poursuit avec le temps atteignant 63 % des patients traités par lamivudine et 71 % des patients traités par adéfovir. Cependant, la survenue de mutations de
Introduction

The goal of therapy for hepatitis B is to improve survival and quality of life by preventing progression of the disease to severe fibrosis, cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma and death. This goal can be achieved if hepatitis B virus (HBV) replication can be suppressed in a sustained manner, as this results in reductions in both histological necroinflammatory activity and the fibrosis of chronic hepatitis. This, in turn, will lower the risk of cirrhosis as well as the risk of hepatocellular carcinoma in non-cirrhotic patients and probably — albeit to a lesser extent — in cirrhotic patients as well [1].

Two different types of drugs can be used in the treatment of chronic hepatitis B: interferon and nucleoside/nucleotide analogs. Analog therapies against HBV belong to three classes:

- L-nucleosides (lamivudine, telbivudine and entecavir);
- deoxyguanosine analogs (entecavir);
- acyclic nucleoside phosphonates (adefovir and tenofovir).

All of these drugs (except emtricitabine) have been approved in Europe for HBV treatment. Their efficacy in reducing HBV replication has been demonstrated in randomized controlled trials lasting 1 year (2 years for telbivudine). Longer-term results (up to 5 years) are available for lamivudine, adefovir, entecavir and telbivudine in patient subgroups [2]. The objective of this report is to review fibrosis regression in these studies in relation to viral suppression and the occurrence of resistance mutation.

Lamivudine and fibrosis regression

Lamivudine results in a rapid decrease in serum HBV DNA concentrations. Using different HBV DNA assays, undetectable HBV DNA was achieved in 1 year in up to 98% with the first-generation assay, and in 36–40% with the more sensitive polymerase chain reaction (PCR) assays in HBeAg-positive patients and around 72% with PCR assays in HBeAg-negative patients [2–5]. Loss of HBeAg was found in 17–33% of patients after 1 year and HBeAg seroconversion was observed in 16–21%. Histology was also markedly improved in over half the patients taking lamivudine compared with placebo (25%). As for fibrosis regression, studies from the late 1990s have shown that, after 1 year of lamivudine, the proportion of patients with worsening fibrosis was significantly lower compared with those taking a placebo [3,4] (Fig. 1). In recent studies where lamivudine was compared with telbivudine or entecavir, Ishak fibrosis scores were improved by 35–61% in HBeAg-positive patients and by 38–46% in HBeAg-negative patients taking lamivudine [6–8].

The histological impact of longer-term treatment with lamivudine has been assessed in two studies [9,10]. With extended therapy, patients are at an increasing risk of developing lamivudine-resistant variants, leading to increased viral replication prior to clinical relapse. In 48 HBeAg-negative patients treated for 2 years with lamivudine, comparisons between the pretreatment and 2-year biopsies demonstrated that, of the 88% of patients with no cirrhosis before treatment, none had progressed to cirrhosis. Of the six patients who had cirrhosis on pretreatment, three showed a significant decrease in fibrosis to the extent that cirrhosis was no longer recognizable in the second specimen. In addition, 50% of patients had no bridging fibrosis prior to treatment but, after 2 years, 17% had progressed to bridging fibrosis, all with the YMDD mutation. After 2 years, of the 18 patients with bridging fibrosis before treatment, eight (44%) showed improvement in bridging fibrosis, two of whom had the YMDD mutation; the remaining 10 patients stayed the same. Despite an extended duration of treatment, the response to lamivudine of the YMDD patients was reduced, and many lost the histological benefits of lamivudine therapy [9]. Of 63 HBeAg-positive patients who took lamivudine for 3 years, 65% developed YMDD mutations. Of the 30% of patients with bridging fibrosis at the start of the study, 63% showed an improvement in bridging fibrosis, although the proportion was higher (83%) among those without, compared with those with, YMDD variants (50–56%). Of the 70% of patients with no bridging fibrosis before treatment, 9% had progressed to bridging fibrosis and 3% to cirrhosis — and all had the YMDD mutation. Indeed, of the 11 patients who had evidence of cirrhosis prior to treatment, eight (73%) showed an improvement of cirrhosis, and five had a decrease in fibrosis score from 4 to 3, two went from 4 to 1 and one went from 4 to 0.

This study demonstrated that 3 years of lamivudine therapy reduced fibrosis and reversed fibrosis (including cirrhosis) in most patients. The emergence of YMDD variants, however, blunted the histological response. This means that patients with the YMDD mutation undergoing extended lamivudine therapy need to be given additional therapies to maintain the histological benefits of treatment [10].

Adefovir dipivoxil and fibrosis regression

Adefovir dipivoxil has proved effective against HBeAg-positive and HBeAg-negative chronic hepatitis B in randomized controlled trials [11,12]. In HBeAg-positive patients, adefovir treatment led to undetectable HBV DNA with PCR assays in 21% of patients after 1 year, while 24% showed HBeAg loss and 12% had seroconversion to HBe antibodies [11]. In a small subset of patients who took adefovir for 5 years, undetectable HBV DNA was observed in 39% of patients, 58% showed HBeAg loss, 48% had confirmed HBeAg seroconversion and 2% had HBsAg loss with seroconversion...
to HBs antibodies [13]. After 1 year of treatment, ranked assessment of liver biopsies showed greater improvement in necroinflammatory activity and fibrosis (41% vs 24%), and less worsening of fibrosis (11% vs 26%; $P < 0.01$), in the adefovir-treated patients compared with the placebo group [11].

These results were confirmed in a recent 1-year trial comparing adefovir and tenofovir in which only 3% of patients taking adefovir saw their fibrosis worsen [14] (Fig. 2). Moreover, in a long-term (5-year) study of adefovir in which 15 patients had liver biopsies before treatment and after 5 years, ranked assessment scores of their paired biopsies showed improvement in fibrosis in 60% [13].

In HBeAg-negative patients, adefovir led to undetectable HBV DNA on PCR assays (< 400 copies/mL) in 51% of patients after 1 year [12]. Long-term therapy with adefovir improved the decrease in serum HBV DNA, with HBV DNA less than 1000 copies/mL in 71% of patients at 2 years, in 79% at 3 years and in 67% at 5 years [15,16].

In the six (5%) patients who had HBsAg loss after a median duration of 196 weeks of adefovir treatment, five showed seroconversion to HBs antibodies. After 1 year of treatment, ranked assessment of paired liver biopsies demonstrated greater improvement in fibrosis (48% vs 25%) and less worsening of fibrosis (4% vs 38%; $P < 0.001$) in those treated with adefovir vs placebo [12]. With long-term therapy with adefovir (up to 5 years), the proportion of patients who experienced at least a 1-point improvement in their Ishak fibrosis score increased from 35% after 48 weeks to 55% and 71% after 192 and 240 weeks of treatment, respectively (Fig. 3).

**Figure 1** Improvement of liver fibrosis at 1 year according to various scoring systems with lamivudine (Lam) treatment compared with placebo (Plb).

**Figure 2** Improvement of fibrosis at 1 year with adefovir (ADV), tenofovir (TDF) and placebo (Plb).
As regards fibrosis regression, among the patients with marked pretreatment bridging fibrosis or cirrhosis and Ishak fibrosis scores of 4–6, the Ishak scores improved by between 0 and 3 in 68% of HBeAg-positive and 56% of HBeAg-negative patients. In contrast, among patients with baseline Ishak fibrosis scores of 0–3, progression of fibrosis to a score greater than 3 after 1 year of treatment was seen in only 1% [6]. However, telbivudine-resistant mutations were seen in 4 and 22% of patients after 1 and 2 years of treatment, respectively [6,17,18]. So far, no data are available regarding fibrosis evolution among these patients.

**Entecavir and fibrosis regression**

Entecavir has proved effective against HBeAg-positive and HBeAg-negative chronic hepatitis B, with a good resistance profile in randomized controlled trials [7,8]. In lamivudine-refractory patients, entecavir has been shown to be effective after 1 year, although extended duration of treatment led to a high rate of resistance mutation that, in turn, led to virological rebound [19].

In naive patients, 1 year of entecavir led to undetectable HBV DNA on PCR assays (<300 copies/mL) in 67% of HBeAg-positive and 90% of HBeAg-negative patients, rates that are significantly higher than those seen with lamivudine (36 and 72%, respectively). In all, 22% of patients had HBeAg loss and 21% had seroconversion to HBe antibodies. HBsAg loss was seen in 2% of HBeAg-positive patients and in one (0.3%) HBeAg-negative patient [7,8]. In lamivudine-refractory patients, entecavir resulted in undetectable HBV DNA in 55% of patients; 10% of patients had HBsAg loss and 8% had seroconversion to HBe antibodies [19].

After 1 year of entecavir treatment, improvement compared with pretreatment histology according to Ishak fibrosis scores (greater or equal to a 1-point decrease) were seen in 39% of HBeAg-positive patients, 36% of HBeAg-negative patients and 34% of lamivudine-refractory patients. In 8% of HBeAg-positive patients, 12% of HBeAg-negative patients and 11% of lamivudine-refractory patients, the Ishak scores worsened [7,8,19]. Among patients with advanced liver fibrosis or cirrhosis treated with entecavir, improvement in Ishak scores after 1 year was observed in 57% of HBeAg-positive patients, 59% of HBeAg-negative patients and 43% of lamivudine-refractory patients [20] (Fig. 4). These values are higher than those seen in the total population treated with entecavir. Furthermore, no worsening of Ishak fibrosis scores was observed in HBeAg-positive and lamivudine-refractory patients with advanced liver fibrosis or cirrhosis, while Ishak scores worsened in only 2% of HBeAg-negative patients with advanced liver fibrosis or cirrhosis. Although the entecavir resistance profile is good, with 1.2% resistance mutation after 5 years, no data are available on the evolution of fibrosis in this population.

**Tenofovir disoproxil fumarate and fibrosis regression**

Tenofovir has also been shown to be effective against HBeAg-positive and HBeAg-negative chronic hepatitis B, with an excellent resistance profile in randomized controlled trials.
In naive patients, 1 year of tenofovir resulted in undetectable HBV DNA on PCR assays (< 400 copies/mL) in 76% of HBeAg-positive and 93% of HBeAg-negative patients, percentages significantly higher than seen in the adefovir group (13 and 63%, respectively). In addition, 21% had seroconversion to HBe antibodies, and HBsAg loss occurred in 3.2% of HBeAg-positive patients and in none of the HBeAg-negative patients[14].

Histological improvement, defined as at least a 2-point reduction in Knodell necroinflammatory score and no worsening in the Knodell fibrosis score, was observed in 74% of HBeAg-positive and 72% of HBeAg-negative patients. Worsening of the Knodell fibrosis score was seen in 2% of HBeAg-positive and 6% of HBeAg-negative patients[14].

Assessment of liver fibrosis

Liver biopsy is still recommended for determining the degree of necroinflammation and fibrosis in the pretherapeutic assessment of hepatitis B[2]. However, the size of the needle biopsy needs to be large enough to precisely determine the degree of liver injury and fibrosis, and the technique is invasive, costly, and subject to sampling error and poor intra- and interobserver concordance[21—27]. Yet, although liver biopsy remains the primary endpoint tool for efficacy assessment in registered studies because of the lack of a correlated equivalent test, there is growing interest in the use of non-invasive methods, such as serum markers and transient elastography, to assess hepatic fibrosis to complement or even avoid liver biopsy[2].

In one retrospective study, Poynard et al. [28] assessed the usefulness of the FibroTest—ActiT est (FT—AT) as a non-invasive marker of histological change in patients with chronic hepatitis B. A total of 462 patients in two randomized trials of adefovir vs placebo with available paired liver biopsies and FT—AT at baseline and after 48 weeks of treatment were studied. The predictive value of FT—AT was assessed using the area under the receiver operating characteristic curves (AUROCs) for the diagnosis of bridging fibrosis, cirrhosis and moderate-to-severe necroinflammatory activity. The impact of treatment with adefovir vs placebo on liver injury was assessed according to baseline stage and virological response at week 48. Analysis of 924 estimates for the diagnosis of bridging fibrosis, cirrhosis and moderate-to-severe necroinflammatory activity yielded FT—AT AUROCs of 0.76 ± 0.02, 0.81 ± 0.02 and 0.80 ± 0.01, respectively. Similar effects of adefovir on liver fibrosis and necroinflammatory activity were observed with both paired liver biopsy and paired biomarkers[28]. Similar diagnostic values for FT—AT have been observed in comparison to three previous studies[29—31].

Furthermore, in a longitudinal assessment of FT—AT during 2-year lamivudine therapy in 283 patients with chronic hepatitis B infection, Poynard et al. [30] found that lamivudine therapy decreased fibrosis in three phases: there was marked improvement during the first six months, then a plateau between 6 and 12 months, followed by another phase of improvement between 12 and 24 months. According to liver biopsy, the emergence of the YMDD variant was associated with higher necroinflammatory activity after 2 years[30].

These studies demonstrate that FT—AT indices may be used as surrogate markers of liver biopsy for both the initial decision to biopsy and for the follow-up of chronic hepatitis B patients.

Recently, Nalpas et al. [32] assessed, in a retrospective study, the accuracy of the FIB-4 index — a simple non-invasive and inexpensive biomarker of fibrosis — as a non-invasive marker of histological change in patients with chronic hepatitis B. A total of 463 patients in two randomized trials of adefovir vs placebo with available paired liver biopsies and FIB-4 index at baseline and after 48 weeks of treatment were included. The AUROCs at baseline to
exclude bridging fibrosis and cirrhosis were 0.76 and 0.81, respectively. The variation of the FIB-4 index correlated with the variation of fibrosis assessed by liver biopsy. It appears that the FIB-4 index is also a helpful tool for assessing fibrosis before and during treatment.

Conclusion

There is considerable evidence that HBV treatment with analogs improves liver fibrosis and histological activity. Despite the use of different definitions of fibrosis regression across studies, no significant differences in fibrosis improvement were found after 1 year of treatment with the five approved drugs currently available in Europe. Despite a higher rate of undetectable HBV DNA among HBeAg-negative, compared with HBeAg-positive, naive patients, there was no major difference in improvement of fibrosis between the two groups after 1 year of treatment. However, long-term treatment is mandatory with analogs in the vast majority of patients with chronic hepatitis B requiring therapy. Studies of long-term treatment with lamivudine and adefovir have shown that fibrosis improvement continues over time and can even lead to cirrhosis regression, but they also demonstrated that development of antiviral drug resistance is a major problem with long-term treatment. As the emergence of resistance blunts the histological response, it is essential that such resistance be identified as early as possible before clinical breakthrough to allow adaptation of the treatment by adding a second drug without cross-resistance, the only efficient strategy in such a scenario.

Long-term treatment of hepatitis B with analogs needs to use the most potent drugs with optimal resistance profiles as first-line monotherapy — namely, tenofovir or entecavir — to maintain fibrosis improvement [2]. Although liver biopsy remains the primary endpoint tool for efficacy assessment in registered studies, there is growing evidence that non-invasive methods of fibrosis diagnosis are likely to become important tools as surrogate markers of liver biopsy both in taking the initial decision to do a biopsy and in the follow-up of chronic HBV patients. As for chronic hepatitis C, new guidelines need to be discussed, taking into account the respective benefit-risk ratios for biopsy, validated biomarkers and elastography [33].

Conflicts of interest

M. Bourlière, A. Kahloun and G. Gascou-Tessonier have no conflicts of interest.

References


