Background: Up to 10% of the HIV-positive population is coinfectected with hepatitis B virus (HBV). Generally, combined treatment includes agents against both viruses, such as lamivudine (3TC). However, HBV resistance to 3TC is high. Adefovir dipivoxil (ADV) has shown its efficacy for treating 3TC-resistant (3TC-R) HBV in HIV-coinfected patients. ADV combined with pegylated interferon (PEG-IFN) has never been evaluated in this population.

Methods: HIV–HBV-coinfected patients with positive HBV e antigen (HBeAg), documented 3TC-R HBV mutation and antiretroviral treatment including 3TC were selected and received ADV (10 mg daily) and PEG-IFN-α2a (180 µg weekly) for 48 weeks.

Results: Of 18 eligible patients (n=16 [89%] male, mean ±sd age 40.45 ±4.82 years), 17 were treated for 48 weeks. One stopped IFN treatment because of adverse events and continued ADV only. The median (interquartile range) HBV DNA at baseline was 8.0 (5.30–8.97) log10 copies/ml and the median (95% confidence interval [CI]) decrease after 48 and 72 weeks was 3.6 (4.9–2.4) and 1.4 (-5.0–2.2) log10 copies/ml, respectively. None of the patients became HBeAg-negative. Median (95% CI) decrease of serum alanine aminotransferase was 27.8 (-66.2–10.5) IU/ml after 48 weeks and 93.0 (-80.0–26.1) IU/ml after 72 weeks.

Conclusions: ADV and PEG-IFN is safe and effective for treating 3TC-R HBV in HIV patients. However, on-treatment response was not maintained off therapy and did not lead to HBV seroconversion. The combination had no effect on HIV disease progression.

Introduction

With more than 400 million people worldwide who are chronically infected and accounting for an estimated one million deaths annually, hepatitis B virus (HBV) infection poses a serious global health problem [1]. The incidence of HBV in HIV-infected individuals varies from 5–10% in Europe and the United States [2,3] and up to 20–30% in Asia and parts of sub-Saharan Africa [4,5]. High levels of HBV replication or HBV e antigen (HBeAg) seropositivity is common in HIV–HBV-coinfected individuals. These two conditions might be predictive of a poor survival. Progression to cirrhosis, liver decompensation, hepatocellular carcinoma and liver-related mortality might be higher in HIV–HBV-coinfected patients compared with HBV-monoinfected patients [6].

Five drugs have been approved for the treatment of chronic hepatitis B (CHB). These include pegylated interferon-α2a (PEG-IFN-α2a; 180 µg weekly for 48 weeks), lamivudine (3TC; 100 mg daily), adefovir dipivoxil (ADV; 10 mg daily), entecavir (0.5 or 1 mg daily) and telbivudine (600 mg daily). In addition, tenofovir disoproxil fumarate (TDF; 300 mg daily), an anti-HIV nucleotide analogue, has demonstrated its safety and efficacy against HBV [7,8] and was approved recently.

Because 3TC is effective against both HBV and HIV, it has almost always been included as a single anti-HBV agent in the antiretroviral regimen of patients coinfected with HIV and HBV. However, up to 90% of HIV–HBV-coinfected patients treated with 3TC monotherapy are at risk of developing HBV resistance to 3TC after 4 years of...
therapy [9]. Prior to the availability of TDF, treatment of 3TC-resistant (3TC-R) HBV in HIV-coinfected patients was limited. ADV is active against wild-type and 3TC-R HBV [10–12] in both HBV–HIV-coinfected and HBV-monoinfected patients. In 3TC-R HIV–HBV-coinfected patients the long term use of ADV added to an antiretroviral regimen including 3TC showed a continuous serum HBV DNA decline over 3 years of therapy [13]. Moreover, no ADV resistance was identified after 3 years and tolerability was excellent.

PEG-IFN has been associated with higher HBeAg seroconversion rates in HBV-monoinfected patients compared with 3TC monotherapy [14]. No such data exist in 3TC-R patients. As previously shown, HBV genotype in HIV-infected patients is predominantly A [15] and is associated with a greater efficacy of PEG-IFN therapy compared with genotype D in HBV-monoinfected patients [14]. Therefore, PEG-IFN could be an interesting treatment alternative in this population [15]. Moreover, the combination of 3TC and PEG-IFN resulted in higher rates of HBeAg and HBV s antigen (HBsAg) seroconversion, virological suppression and biochemical response among patients with HBeAg-positive CHB than 3TC alone [14]. The combination of PEG-IFN with an oral anti-HBV drug might be attractive and could be used as a first-line therapy in HBeAg-positive patients because of a potent higher rate of HBeAg seroconversion and subsequent limited duration of therapy. New therapeutic strategies in difficult-to-treat HIV coinfected, including those patients with HBV 3TC-R mutations and without indication for antiretroviral treatment are therefore important to develop.

In this study we explored the efficacy and safety of a combination therapy with ADV and PEG-IFN in 3TC-R HBV–HIV-coinfected patients.

Methods

Study design

This pilot, open-label study was conducted to evaluate the efficacy and safety of a combination therapy of ADV with PEG-IFN-α2a for the treatment of 3TC-R HBV in HIV-coinfected patients. Those with proven HBV DNA polymerase mutations that conferred HBV resistance to 3TC received ADV 10 mg daily (taken orally) and PEG-IFN 180 µg weekly for 48 weeks. ADV plus PEG-IFN were added to the pre-existing antiretroviral regimen that contained 3TC. Safety visits were held every 4 weeks to monitor haematological parameters, liver function, renal function and physical or psychological symptoms. Changes in serum HBV DNA, HIV RNA and CD4+ T-cell count were assessed every 12 weeks. After the 48-week treatment course, patients were followed up for 24 weeks.

The primary study endpoint was the rate of HBeAg seroconversion to anti-HBe. Secondary objectives assessed the change in serum HBV DNA from baseline to week 48, alanine aminotransferase (ALT) flares (defined as rise in ALT levels according to the baseline levels) and changes in creatinine levels.

The study protocol and amendments were approved by the local institutional review board and ethics committees and all patients gave written informed consent.

Patients

All patients were HIV–HBV-coinfected. Inclusion criteria were age >18 years, HIV plasma load <2.6 log10 copies/ml (Cobas Amplicor HIV-1 Monitor, Roche, Meylan, France; lower limit of quantification [LLQ] 2.3 log10 copies/ml), CD4+ T-cell count >200 cells/µl, stable antiretroviral therapy that included 3TC (150 mg twice daily) for at least 3 months prior to baseline, confirmed infection with 3TC-R HBV as defined by the presence of a 3TC-R mutation in the polymerase encoding gene, baseline HBV DNA >5 log10 copies/ml (Cobas Amplicor HBV Monitor 2.0, Roche; LLQ 2.3 log10 copies/ml), serum HBeAg-positive and HBV e antibody (HBeAb)-negative (AxSYM, Abbott Diagnostics, Les Ulis, France), availability and willingness to provide written informed consent. Exclusion criteria were use of ADV in the 24 weeks prior to baseline, use of PEG-IFN in the 24 weeks prior to baseline, coinfection with HCV or hepatitis delta virus, new AIDS-defining event diagnosed within 4 weeks prior to baseline, treatment with immunomodulator drugs (IFNs, IL2 or corticosteroids) in the 4 weeks prior to baseline, anti-HBV therapy (IFN-α, famciclovir, TDF, foscarinet, ganciclovir or lobucavir) in the 12 weeks prior to baseline, history of clinically significant renal dysfunction within the 12 months prior to baseline, severe hepatic dysfunction or decompensated cirrhosis (Child–Pugh score >5), history of hepatic encephalopathy, history of variceal bleeding, ascites, sonographic suspicion of hepatocellular carcinoma or alpha foeto protein >50 ng/ml, concomitant therapy with aminoglycosides, amphotericin B, cidofovir, cis-platinum, intravenous pentamidine, vancomycin, systemic chemotherapeutic agents, d-carnitine and d-1-carnitine, pregnancy or breastfeeding and history of autoimmune hepatitis.

Viral parameters

HBV serum markers (HBeAg and anti-HBeAb) were determined by Abbott’s AxSYM test (Abbott Diagnostics). Serum HBV DNA was measured by PCR (Cobas Amplicor HBV Monitor 2.0, Roche; LLQ 2.3 log10 copies/ml). Serum was diluted to allow quantification of samples above the upper limit of quantification (200,000 copies/ml). HIV RNA was assessed by a commercial assay (Amplicor HIV-1 Monitor 1.5, Roche; LLQ 2.3 log10 copies/ml). HBV 3TC-R mutations were detected using a...
first generation line probe assay as previously described [16]. 3TC-R was defined by the detection of at least one amino acid change at position rtM204.

Variables were expressed as mean (±sd) or medians (95% confidence interval [CI]) as appropriate. Two-sided P-values <0.05 were deemed statistically significant. Analyses were performed using NCSS 2004 software (Kaysville, UT, USA).

Results

Baseline characteristics
Table 1 summarizes the baseline characteristics of the 18 HIV–HBV-coinfected patients included in the study. In total, 16 patients were male with a mean age of 40.45 ±4.82 years. The main risk factor for viral infections was sexual transmission in 17 cases (94%) and intravenous drug use in one case (6%). The median duration of HIV infection was 10.4 years (95% CI 8.96–14.31). All patients were on a stable antiretroviral treatment consisting of two nucleoside analogues including 3TC and one protease inhibitor. Antiretroviral therapy remained unchanged in all patients throughout the study period. The median HIV viral load was 2.52 log_{10} copies/ml (interquartile range [IQR] 2.00–2.89) and the median CD4+ T-cell count was 441 cells/mm³ (IQR 299–557).

The median HIV viral load at baseline was 8.0 log_{10} copies/ml (IQR 5.30–8.97). All patients showed 3TC-R mutations as defined by the detection of at least one amino acid change at position rtM204. The distribution of mutations included rtL180M and rtM204V in 16 patients and rtL180M and rtM204V/I in two patients.

The median ALT level at baseline was 78 IU/l (IQR 60–118) and two patients had normal ALT. The median creatinine level was 86.5 µmol/l (IQR 76–94).

Safety
A total of 17 patients completed the 48-week treatment course with PEG-IFN 180 µg weekly (subcutaneous) and ADV 10 mg daily (oral). One patient discontinued prematurely at week 4 because of asthenia and continued on ADV only. This patient was excluded from the efficacy analysis. There were no serious adverse events reported. All 17 remaining patients complained about mild asthenia from week 2, which was attributed to IFN therapy, but no significant mood changes were reported. One patient had erythema at the injection site during the first 4 weeks of treatment. No patient had liver decompensation. Platelet count and neutrophil count dropped slightly during treatment and returned to baseline in the follow-up period. Dose reduction of PEG-IFN and growth factor use were not needed in any of the patients. No changes in serum creatinine levels were observed in this study (Figure 1).

An ALT flare was observed at week 4. ALT reached a median level of 170 IU/l (IQR 65–194) and then returned to normal levels during the follow-up period. ALT flares were not associated with liver decompensation or alteration of liver synthesis tests (bilirubin and prothrombine time). At week 72, the median ALT level was 35 IU/l (IQR 28–52) and 6 of 17 patients (35%) had ALT levels below the upper limit of the normal range compared with two patients at baseline (Figure 1). Three patients flared after cessation of treatment but had normalized ALT levels at week 72.

There was no evidence of loss of HIV control during the study. The CD4+ T-cell count dropped non-significantly on treatment and returned to baseline off therapy.

Efficacy
One study endpoint was to assess the HBcAg or HBsAg seroconversion rate of treatment with PEG-IFN and

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mean age, years (±sd)</td>
<td>40.45 ±4.82</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>16 (89)</td>
</tr>
<tr>
<td>Risk factors for HIV</td>
<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>17 (94.4)</td>
</tr>
<tr>
<td>Intravenous drug use, n (%)</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Median HIV duration, years (95% CI)</td>
<td>10.4 (8.96–14.31)</td>
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<tr>
<td>Median HIV viral load, log_{10} copies/ml (95% CI)</td>
<td>2.52 (2.3–2.8)</td>
</tr>
<tr>
<td>Median CD4+ T-cell count, cells/mm³ (95% CI)</td>
<td>441 (298–544)</td>
</tr>
<tr>
<td>Median HBV viral load, log_{10} copies/ml (95% CI)</td>
<td>8.0 (5.3–8.97)</td>
</tr>
<tr>
<td>Median ALT level, IU/l (95% CI)</td>
<td>78 (60–118)</td>
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</table>

ALT, alanine aminotransferase; CI, confidence interval; HBV, hepatitis B virus.

Figure 1. Changes in median ALT and median creatinine levels during treatment and follow-up of 17 HIV–HBV-coinfected patients treated with ADV and PEG-IFN

ADV, adefovir dipivoxil; ALT, alanine aminotransferase; HBV, hepatitis B virus; PEG-IFN, pegylated interferon.
ADV in HIV–HBV-coinfected patients with 3TC-R HBV. Unfortunately, none of the 17 patients who completed the 48-week treatment course had HBeAg or HBsAg seroconversion at the end of treatment or at the end of the 24-week follow-up period.

Figure 2 shows the changes in HBV DNA during treatment and follow-up. There was a significant on-treatment reduction from baseline in HBV viral load of 4.35 log10 copies/ml to 3.65 log10 copies/ml (95% CI 2.49–4.30) at week 48 ($P=0.001$). However, at the end of the follow-up period HBV DNA returned to pre-treatment levels with a median of 7.3 log10 copies/ml (IQR 4.76–9.57). Two patients had undetectable HBV DNA under the LLQ of 2.3 log10 copies/ml by week 48, one by week 60 and none at the end of follow-up (week 72).

No on-treatment serum HBV DNA breakthrough (1 log10 copies/ml increase from nadir) was observed.

Discussion

Although conducted without a control arm and with a small number of patients included, the results of this study were able to demonstrate the antiviral efficacy of a combination therapy of ADV and PEG-IFN in HIV–HBV-coinfected patients with 3TC-R HBV. The combination treatment resulted in a significant reduction in serum HBV DNA levels after 48 weeks of treatment compared with baseline. HBV DNA suppression was associated with a reduction in ALT serum levels. However, HBV returned to baseline values during the 24-week off-treatment follow-up period. Efficacy and safety of ADV in HIV–HBV-coinfected individuals with 3TC-R HBV have been reported with an HBV DNA decline of 4.68, 5.24 and 5.90 log10 copies/ml after 1, 2 and 3 years, respectively [13]. HBV DNA reduction resulted in improved liver histological damages, including fibrosis, ALT normalization and clinical improvement. Moreover, HBV DNA suppression was associated with HBeAg seroconversion in 7% of the coinfected patients after 3 years of ADV therapy [13]. Seroconversion to anti-HBe occurred in about 12% of HBV-monoinfected patients after 48 weeks of ADV [11].

PEG-IFN has even shown a seroconversion rate of >30% in HBV-monoinfected patients [14], especially in patients with HBV genotype A, a low viral load and increased transaminase levels. Response rates in the HIV setting have not yet been investigated. Almost all the studies conducted on HIV–HBV-coinfected patients concluded that there was a reduced response to standard IFN-α2a compared with HBV-monoinfected patients [17–22]. However, endpoints were heterogeneous and the numbers of patients included were small. Furthermore, these studies were performed in immunosuppressed patients not receiving potent anti-HIV therapy. Although anticipated, the antiviral activity of PEG-IFN in 3TC-R HBV is yet unknown.

The most beneficial effect expected of IFN treatment in HBV, namely HBeAg seroconversion to anti-HBe, was not observed in this study. HBeAg seroconversion is a key objective of therapy in HBeAg-positive patients with CHB because it is associated with improved long-term clinical outcomes (such as improved liver histology and increased complication-free and overall survival) [23,24].

A previous study [14] showed that the combination of 3TC and PEG-IFN leads to higher rates of HBeAg seroconversion and HBV DNA suppression than 3TC monotherapy in HBeAg-positive HBV-monoinfected patients, but did not show higher rates compared with PEG-IFN alone. We presumed an additional effect in our population that was not observed. Our results are comparable to those observed in ADV monotherapy in HIV–HBV-coinfected patients, and a beneficial effect of the addition of PEG-IFN treatment could not be described. The immunological effect of PEG-IFN that could play a role in HBeAg seroconversion was not observed and might be impaired in HIV patients (although their immune system has been stabilized by HIV treatment) compared with the non-HIV population. However, no strong conclusion can be formulated from the results of our study because there was no control arm and, more importantly, the number of included patients was small. Although needed, larger trials could be difficult to carry out in developed countries as almost all HIV–HBV-coinfected patients have TDF plus 3TC or emtricitabine included in their antiretroviral regimen, which is one of the most effective

Figure 2. Changes in median HBV DNA during treatment and follow-up of 17 HIV–HBV-coinfected patients treated with ADV and PEG-IFN

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ADV, adefovir dipivoxil; HBV, hepatitis B virus; LLQ, lower limit of quantification; PEG-IFN, pegylated interferon.
anti-HBV regimens currently available. Nevertheless our study indicates the antiviral efficacy and tolerability of a combination therapy including an oral anti-HBV agent with PEG-IFN.

Encouraging results on the tolerability of PEG-IFN-based therapy in HIV–HBV-coinfected patients were observed. The most common side effect associated with IFN was asthenia, resulting in a withdrawal of PEG-IFN in only one case. Haematological changes were mild and growth factor use was not necessary during the study period. PEG-IFN had no effect on HIV disease and changes in CD4+ T-cell count were moderate and transient. There was no evidence of loss of antiretroviral efficacy over the study period and all patients remained on their pretreatment regimen. Furthermore, no modification of any of the antiretrovirals was needed throughout the study period. The tolerability results are encouraging, taking into account a possible longer duration (for example, 96 weeks) of PEG-IFN treatment that might be needed in HIV–HBV-coinfected individuals.

A substantial reduction of serum ALT levels compared with baseline was observed. Initial and transient ALT flares were not associated with liver decompensation or liver function test alteration. Interestingly, reduced serum ALT level was maintained off therapy.

The choice of anti-HBV treatment in HIV–HBV-coinfected patients is usually based on the indication for an antiretroviral treatment. Because TDF has proven its non-inferiority to ADV for the treatment of HBV in HIV-coinfected patients [7], it would be the drug of first choice in combination with 3TC in coinfected patients with high serum HBV DNA who need antiretroviral therapy [25]. In contrast, agents coinfected patients with high serum HBV DNA who had no activity against both HIV and HBV should be avoided when therapy is only needed for HBV because of concerns over the development of HIV drug resistance [26]. As concerns have been raised over the use of entecavir in untreated HIV patients because of the possible emergence of 3TC-R HIV [27] and the reduced efficacy in 3TC-R HBV, ADV might play an important role in this setting. A theoretical risk for developing mutation K65R has not been demonstrated [26], but all patients in our study were on suppressive highly active antiretroviral therapy regimens. PEG-IFN, as an effective and safe agent, should still be taken into consideration [25].

In conclusion, ADV plus PEG-IFN is safe and effective for the treatment of 3TC-R HBV in HIV-coinfected patients. However, on-treatment response is not maintained off therapy and did not lead to HBV seroconversion. The combination has no effect on HIV disease progression. Studies are needed to assess the role of PEG-IFN for the treatment of HBV in HIV-coinfected patients.

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Disclosure statement

The authors declare no competing interests.

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