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REVIEW

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Management of hepatitis B in patients coinfected with the human immunodeficiency virus

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Abstract The human immunodeficiency virus (HIV) and the hepatitis B virus share common routes of transmission, and hence, coinfection with these two viruses is common. Chronic hepatitis B does not influence the progression of HIV disease or the response to highly active antiretroviral therapy. It is clear, however, that HIV infection does impact the course of hepatitis B, as higher rates of chronic carriage, lower seroconversion rates, and accelerated progression towards cirrhosis have been observed. Vaccination against hepatitis B is less effective in HIV-infected individuals. Coinfected subjects have a poor response to interferon therapy. Lamivudine is more effective in coinfected subjects but must not be used as monotherapy because of the risk of resistance developing. Combination therapy with lamivudine and tenofovir has shown promise and is currently being investigated in clinical trials, while new drugs and other combinations are in development.

Introduction

The prognosis for individuals infected with the human immunodeficiency virus (HIV) has been improved considerably since the introduction of highly active antiretroviral therapy (HAART) [1]. One of the consequences of longer survival is that many individuals coinfected with hepatitis B and C are developing chronic liver disease. There is clear evidence that the morbidity and mortality associated with chronic hepatitis in HIV-infected patients is increasing [2–6].

It is important to prevent hepatitis B infection or, if the infection is established, to implement effective treatment to prevent the progression of chronic viral hepatitis. The optimal management of HIV and hepatitis B coinfection is unclear and requires further study. The purpose of this review is to update the clinician on recent developments and outline current management strategies.

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Epidemiology

HIV and hepatitis B virus (HBV) share several common routes of transmission. Both viruses can be transmitted sexually, vertically, and by exposure to infected blood (e.g. during transfusions or intravenous drug use) or other body fluids. Currently, there are approximately 42 million HIV-infected people and over 350 million hepatitis B carriers worldwide.

In the UK, there are over 25,000 individuals receiving care for HIV infection [7]. More than 80% of HIV-infected individuals have evidence of past or persistent HBV infection, and 8–11% are chronic carriers as defined by the persistent presence of hepatitis B surface antigen (HBsAg) [8]. The main risk groups for coinfection are men who have sex with men, intravenous drug users, and individuals from areas with a high prevalence of HBV. In Africa, for example, there are high rates of HBsAg carriage (up to 13%) [9], which is of importance since Africans now form the largest group of newly diagnosed HIV-positive individuals in the UK.

Natural history of hepatitis B virus infection

HBV, a DNA virus belonging to the family of hepadnaviruses, primarily targets hepatocytes. Acute infection with HBV leads to a cytotoxic T lymphocyte response directed at the infected hepatocytes. In the majority of patients (approximately 90%), this cytotoxic T lymphocyte response leads to successful virus clearance. These individuals clear HBsAg and develop antibodies to hepatitis B surface antigen (anti-HBs), which confer long-lasting immunity. In a small proportion of patients (<1%), a heightened immune response leads to fulminant hepatitis and liver failure. In the remaining 10%, there is a

suboptimal host immune response that can cause progressive hepatitis and cirrhosis. A further consequence is the development of hepatocellular carcinoma, although the exact pathogenic mechanisms are unclear. The mechanism of the hepatic damage in chronic HBV infection relates to the recognition of antigens on HBV-infected hepatocytes by CD8+ lymphocytes and direct cell killing by these lymphocytes. HBV itself in most circumstances is not cytopathic, and the liver damage is primarily related to the degree of immune response.

The natural history of chronic hepatitis B is often defined by serological markers. An important step in chronic HBV infection is HBeAg seroconversion, which has generally been regarded as corresponding to a transition from active viral replication to a less active carrier state. This is characterised by the clearance of HBeAg from serum followed by the appearance of anti-HBe antibodies. This rate of HBeAg seroconversion in untreated HIV-negative individuals is about 8–12% per year [10].

New technologies have challenged conventional wisdom regarding the natural history of infection. Sensitive HBV-DNA assays have identified HBV DNA in the presence of antibody to hepatitis B core antigen (anti-HBc) but have found an absence of other markers of viral replication, i.e. HBsAg [11]. This has been termed occult hepatitis B. The clinical implications of occult hepatitis B are unclear at present, but this form of hepatitis has been documented in those with HIV infection [12, 13]. It has been postulated that the finding of occult hepatitis B in HIV-infected patients may just demonstrate the increased sensitivity of PCR-based testing in comparison with serological assays, that occult hepatitis B might be due to genetic mutations of HBV, or that this form of hepatitis B might represent another clinical stage determined by the host immune response to HBV. Others have suggested that occult hepatitis B may represent subclinical reactivation. Studies are required to assess whether the presence of HBV DNA in occult hepatitis B contributes to the progression of liver disease.

Impact of hepatitis B virus on human immunodeficiency virus infection

There is evidence from molecular studies that HBV could have a direct effect on HIV at the cellular level [14]. The data from clinical studies are mostly from the pre-HAART era and are less clear [15–21]. Only one study showed an increased risk of developing AIDS in patients coinfected with HIV and HBV, but this did not study chronic hepatitis B: the study group members were anti-HBc positive, but the majority were HBsAg-negative [15]. Most prospective studies have shown no significant effect of HBV infection on the progression of HIV disease [18–21].

More recent studies in the HAART era have looked at HIV disease progression and the response to HAART in patients with chronic hepatitis B. Thio et al. [22] analysed the Multicenter AIDS Cohort Study and found that, amongst patients in whom HAART was initiated, viral loads were reduced to undetectable levels in similar proportions of HBsAg-positive and HBsAg-negative individuals, and there was no significant difference between the groups in the increase in CD4+ lymphocyte counts. Two recent prospective studies have shown no impact of hepatitis B status on clinical progression of HIV infection or on virological and immunological response to HAART [23, 24]. An Italian study showed HBsAg carriers in whom HAART was initiated had an increased risk of clinical progression and a reduced rise in CD4+ lymphocyte counts, but neither of these findings reached significance [25].

Impact of human immunodeficiency virus infection and highly active antiretroviral therapy on hepatitis B virus infection

There is little data on the effect of HIV infection on the manifestations of acute HBV infection. Two studies with small numbers have suggested an increased risk of symptomatic illness in HIV-infected individuals, but in both studies the difference was accounted for mainly by nonicteric illness [26, 27].

There is much clearer evidence regarding the risk of progression to chronic hepatitis B. Studies have demonstrated an increased risk of chronic HBV carriage after acute hepatitis B in patients coinfected with HIV [28–31]. Bodsworth et al. [26] found that the risk of chronic carriage was increased in patients with lower CD4+ lymphocyte counts. Several studies have reported that viral replication tends to be higher amongst coinfected individuals, as demonstrated by a higher prevalence of HBeAg and higher levels of HBV DNA [30–38]. There is also clear evidence that the rates of HBV DNA clearance and HBeAg seroconversion are significantly reduced amongst those with HIV infection.

The effect of HIV infection on markers of hepatic inflammation is not clear. Several studies have shown significantly lower levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in HIV-infected patients [21, 35, 36, 38], yet others have shown no difference [30, 33, 39, 40]; one study even suggested a trend towards higher levels [34]. Histological studies seem clearer, with the majority suggesting less severe hepatic inflammation in patients with coinfection [36, 38, 41]. However, two studies suggested an increased risk of progression to cirrhosis in coinfected patients [34, 35]. A significant problem with many of these studies performed in the 1980s is the lack of control for hepatitis C coinfection, for which serological testing had not been introduced.

It is well recognised that the use of HAART can be limited by the development of hepatotoxicity [42, 43]. Several studies have looked at the impact of chronic viral hepatitis on the hepatotoxicity of antiretroviral regimens [44–51]. In all of these studies, the rate of hepatotoxicity is higher amongst both HBV/HIV-coinfected and HCV/HIV-

coinfected patients, and in four studies chronic hepatitis B was identified as an independent risk factor for the development of hepatotoxicity [44, 45, 47, 51]. The studies in which hepatitis B was not an independent risk factor for hepatotoxicity involved small numbers of coinfected patients [46, 48, 49, 50].

There is a risk of HBV reactivation at any stage in the natural history of hepatitis B. This is usually in the form of HBeAg reactivation in HBsAg carriers, although there are also reports of HBsAg reactivation after apparent clearance of HBsAg. Reactivation may be manifested as acute hepatitis or a rise in ALT. There is some evidence that this risk of HBeAg reactivation is increased amongst those concurrently infected with HIV and that the risk is higher amongst those with low CD4+ lymphocyte counts [21]. There are reports of HBsAg reactivation upon the initiation of therapy with protease inhibitors [52] and of HBeAg reactivation with subsequent seroconversion to anti-HBe [53]. This may be a consequence of the recovery of cell-mediated immunity with HAART, which leads to an exacerbation of cytolysis and/or promotes clearance of HBV.

The clinical implication of these findings is that deterioration in liver function or the development of clinical hepatitis after the commencement of HAART may not be related to drug toxicity but instead may reflect HBV-related hepatitis due to immune reconstitution. Patients must therefore be fully assessed so that antiretroviral agents are not discontinued inappropriately.

Prevention of hepatitis B virus infection

Hepatitis B is preventable by vaccination. Inactivated vaccines were first introduced in the 1980s but now have been superseded by recombinant vaccines. Over 95% of healthy individuals will develop protective immunity following three separate doses of hepatitis B vaccine [54]. There is clear evidence, however, that the response to both inactivated and recombinant vaccine is significantly poorer amongst those infected with HIV [55–61]. In addition to poorer initial response, there is a significantly increased rate of loss of protective antibodies. This is more evident in individuals with lower CD4+ lymphocyte counts [58, 61].

Increasing the number of vaccine injections will increase the response rate, although there is still a significant rate of loss of antibodies [61]. Recent guidelines have suggested that up to three boosters should be given after the initial vaccination course to achieve protective antibody levels, and subsequently, anti-HBs levels should be checked annually and further boosters given if necessary [62, 63].

Management of hepatitis B in patients coinfected with human immunodeficiency virus

Initial evaluation

Initial assessment requires clinical staging of both HIV infection and hepatitis B. The need for further investigations and treatment will depend on assessment of both infections. Initial tests should include those to identify markers of HBV replication, i.e. HBeAg and HBV DNA, as well as a full blood count, liver function tests, and measurement of α-fetoprotein, CD4+ lymphocyte count, and HIV RNA levels. Ideally, a liver biopsy should be performed in all patients.

Patients should be counselled about the risks of transmission, and close contacts should be vaccinated for hepatitis B. Patients should be vaccinated against hepatitis A if they are not already immune, and coinfection with hepatitis C virus (HCV) should be excluded. Counselling should also include advice to limit alcohol intake.

Patients not requiring HBV treatment should be regularly monitored with clinical examination, full blood count, liver function tests, and measurement of α-fetoprotein. Evidence of progressive liver disease should prompt repeat tests to detect markers of HBV replication as well as tests to exclude other causes of concurrent liver disease.

Aims of therapy

The aim of drug treatment for chronic hepatitis B is to prevent the long-term complications of cirrhosis and hepatocellular carcinoma. This requires therapies that suppress viral replication. The initial treatment goals, therefore, are the clearance of HBeAg and a reduction in HBV DNA levels. The optimal management of the HBV/HIV-coinfected patient is unclear. Who should be treated, at what stage, and with what regimen are issues that require clarification. We will look first at the evidence supporting the use of the drugs currently used in patients coinfected with HBV and HIV, then discuss the practical issues of clinical management.

Interferon alfa

Interferon treatment for chronic hepatitis B was introduced in the 1980s. Interferon alfa is a cytokine with both antiviral and immunomodulatory effects. A meta-analysis of 15 randomised controlled trials of the use of interferon alfa in HBV monoinfection showed an increase in the seroconversion rate of HBeAg from 12 to 33% after 6–12 months of follow-up [64]. The most important predictors of response to interferon are high ALT and low HBV DNA levels.

Most studies have shown that HBV/HIV-coinfected patients are significantly less likely to seroconvert than HIV-negative patients [65–69]. Often, these data are

confounded by the fact that the HIV-positive patients have had lower baseline ALT or AST levels, which have been shown to be predictors of a poor response to interferon therapy. One study showed that interferon could be effective in HBV/HIV coinfection if used in those with high pretreatment ALT levels [70].

This poor response in association with the significant adverse effects and the knowledge that interferon can lower CD4+ lymphocyte counts has led to limited use of interferon in coinfected individuals. There is hope that the use of pegylated interferon will result in improved outcomes like it has in the management of hepatitis C. Early reports suggest an improved response rate in HIV-negative patients with chronic hepatitis B following treatment with pegylated interferon compared to conventional interferon [71]. No studies to date have looked at its use in a coinfected population.

Lamivudine

Lamivudine (3TC) is an inhibitor of HIV reverse transcriptase. It was developed as an antiretroviral agent and was introduced into practice in 1993 [72]. It has also demonstrated activity against HBV reverse transcriptase in vitro, and studies subsequently revealed activity against HBV replication amongst immunocompetent persons [73].

Early studies suggested that this activity also translated to patients coinfected with HIV. A retrospective analysis of the CAESAR study described significant HBV DNA suppression with lamivudine and increased rates of HBV DNA clearance [74]. Although not significant, there were also trends towards greater reduction in HBeAg levels and lower ALT levels. Subsequent prospective studies have provided supporting evidence of a beneficial effect of lamivudine amongst coinfected persons [75–78].

The most reliable predictor of response to lamivudine in HIV-negative individuals is the pretreatment ALT level [79, 80]. ALT levels less than twice the upper limit of normal lead to HBeAg seroconversion rates of less than 10% at 1 year. No studies have specifically identified predictors of response in coinfected subjects.

The principal problem with lamivudine therapy for chronic HBV infection is the development of viral resistance. Resistance is due primarily to mutants containing amino acid substitutions in the YMDD motif of DNA polymerase. The major resistance genotypes have been identified as M204V together with L180M, and M204I alone or in combination with L180M [81]. Resistance of HBV to lamivudine has been shown to be related primarily to the duration of lamivudine therapy. The incidence of genotypic mutations was 14% at 1 year in HIV-negative individuals [73]. Studies have suggested that the development of resistance is exaggerated in coinfected patients. Most studies have detected a linear relationship in terms of the development of resistance, with an approximate incidence of 20% per year [77, 78, 82, 83]. This manifests clinically as a rebound in HBV DNA levels and a progression of hepatic damage. Clinical recurrence has been reported both when resistance to lamivudine develops and upon withdrawal of lamivudine therapy [84].

Adefovir

Adefovir is a nucleotide analogue that was initially developed as an antiretroviral agent. Its use in HIV infection was limited due to renal toxicity at a dose of 30 mg daily. It has a wide range of antiviral activity and is active against HBV in vitro.

It has now been licensed at a dose of 10 mg daily for use in HIV-seronegative persons with chronic hepatitis B following good evidence of its benefit both in those naïve to therapy and in those in whom resistance to lamivudine has developed [85–87]. Studies have shown that there is no cross-resistance between lamivudine and adefovir [88]. Benefit may also extend to those persons coinfected with HIV, as studies have shown a sustained decrease in HBV DNA levels both in lamivudine-naïve patients and in those previously exposed to lamivudine [89–91].

Adefovir at a dose of 10 mg daily has no significant effect against HIV and theoretically could be given to coinfected patients not requiring antiretroviral therapy. There have been concerns about the potential for development of HIV viral resistance, but one study showed no evidence of adefovir-associated resistance mutations in the HIV reverse transcriptase gene after 12 months of adefovir therapy [92]. However, this study involved small numbers, and all patients were also on lamivudine therapy and harboured M184V lamivudine-associated mutations.

Tenofovir

Tenofovir is a nucleotide reverse transcriptase inhibitor related to adefovir. It has activity against both HIV and HBV in vitro. Studies have shown a reduction in HBV DNA levels and in transaminase levels in coinfected patients with or without previous exposure to lamivudine who were treated with tenofovir [93–100]. There is no evidence of cross-resistance with lamivudine and no evidence of novel mutations in HBV polymerase, although the follow-up period in all studies was short.

Other drugs in development

Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor with demonstrated activity against both HIV and HBV in vitro [101]. It has been approved for use in the USA and in Europe as an antiretroviral agent but not yet as treatment for hepatitis B. Early studies have shown potent suppression of HBV replication and HIV in coinfected patients [102]. There is concern about cross-resistance with lamivudine. Entecavir has shown good activity against HBV both in lamivudine-naïve and lamivudine-experienced patients [103, 104]. Studies are assessing its use in coinfected individuals.

Combination therapy

There is interest in the concept of combination therapy to suppress viral replication and to prevent the emergence of resistance. In coinfection the combination of lamivudine and tenofovir is a potentially attractive option. The combination has proven efficacy in the treatment of HIV infection. In one study, the group that received the combination exhibited greater reduction in both HBV DNA levels and ALT levels and fewer instances of the YMDD mutant than the group treated with lamivudine alone, but the number of patients involved was very small [105].

Practical treatment issues

The clinician will need to take into account the following three main factors when assessing a patient coinfected with HBV and HIV: (i) whether the patient requires antiretroviral therapy for HIV infection; (ii) whether the patient requires anti-HBV therapy; and (iii) the patient's prior exposure to antiviral agents.

The decision whether to initiate antiretroviral therapy should follow standard guidelines for HIV-infected individuals, which are based on the presentation of clinical disease, the CD4+ lymphocyte count, and levels of HIV RNA. There is no convincing evidence that HBV affects the natural history of HIV infection, so there is no rationale for starting HAART earlier in coinfected individuals.

The decision whether to commence anti-HBV therapy will depend on clinical findings in addition to markers of HBV replication, i.e. HBeAg and HBV DNA levels, and markers of hepatic inflammation, i.e. transaminase levels. Ideally, a liver biopsy should be performed in all patients considered for treatment so that the stage of liver disease can be accurately assessed. The indications for liver biopsy are similar in HBV/HIV-coinfected individuals and in those infected with HBV alone; that is, there should be evidence of HBV replicative activity (HBeAg positive/HBV DNA positive). In HIV-negative individuals, an ALT level greater than twice the upper limit of normal is normally regarded as the threshold for considering therapy. ALT levels are consistently lower in coinfected patients and show poor correlation with histological changes. This highlights the importance of liver biopsy in the assessment of the coinfected patient, and liver biopsy should therefore be considered regardless of ALT levels.

The absence of HBeAg does not preclude treatment. Most HBeAg-negative patients have lower levels of HBV DNA. Treatment should be considered in the presence of persistently raised ALT levels or histological evidence of active hepatitis.

If HIV therapy is required but HBV therapy is not, then a regimen that avoids drugs active against HBV should be chosen. This leaves options open in case HBV therapy becomes necessary at a later time. There may be instances in which HBV therapy is required but HIV therapy is not, for example in a patient with a stable, satisfactory CD4+ lymphocyte count. Lamivudine or tenofovir should not be used as monotherapy due to the risk of resistance developing. Interferon could be used in this instance, and further studies on the use of pegylated interferon are awaited with interest. Adefovir could also be used, although there is concern about the development of resistance (of both HBV and HIV), which will also be conferred to tenofovir.

The majority of coinfected individuals will benefit from simultaneous treatment of HIV and HBV and should be commenced on a HAART regimen that contains lamivudine, tenofovir, or both. The risk of resistance developing with lamivudine alone suggests that the combination with tenofovir may become the treatment of choice. There are ongoing clinical trials assessing both drugs alone and in combination as part of a HAART regimen for coinfected individuals and, where possible, patients should be enrolled in these trials.

The evidence at present suggests that lamivudine treatment should be continued even if resistance of HIV develops. Otherwise, there is a risk of precipitating a clinical recurrence upon lamivudine withdrawal. Therefore, if the HAART regimen must be changed due to treatment failure or toxicity issues, then lamivudine should be continued as part of the new regimen. It may be that the same is true for tenofovir, but there is no data to support this.

Another important issue is the course of action to take when lamivudine, as part of a HAART regimen, starts failing in its anti-HBV activity. This is most likely to result from the emergence of resistant virus and will be manifest by a rise in the HBV DNA level, a rise in ALT, or clinical progression of disease. There is some evidence to support the addition of tenofovir in this situation, although ideally this should be done in the context of a clinical trial. The question of whether to continue or stop lamivudine requires further study.

Conclusions

Chronic hepatitis due to hepatitis B and C viruses has become an increasingly important cause of morbidity and mortality in HIV-infected individuals. Although HBV infection does not seem to impact the progression of HIV disease, the presence of HIV infection leads to increased HBV replication and accelerated progression to cirrhosis. We need to learn more about the natural history of hepatitis B infection in coinfected individuals. In particular, further studies on the clinical significance of occult hepatitis B and the effect of HAART on progression of liver disease are required.

There are few therapies currently available for use in HBV/HIV-coinfected individuals, although new drugs are in development. More information on when to start treatment in these patients is needed. Although the aim of therapy is to prevent the progression of liver disease, there is no evidence currently that the treatments we are

using are doing that. Combination therapy is likely to become more common but requires further study. We would encourage all doctors involved in treating HBV/HIV-coinfected patients to enter patients into clinical trials to attempt to answer some of these questions and, hence, in the future, reduce the burden of disease caused by chronic hepatitis B in the coinfected population.

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