Hepatitis Monthly 2008; 8(2): 125-127

REVIEW ARTICLE

Emtricitabine in Chronic Hepatitis B: A Mini Review

Emilio Palumbo*

Clinic of Pediatrics, Hospital of Sondrio, Sondrio, Italy

Emtricitabine is a cytosine nucleoside analog with antiviral activity against both hepatitis B virus (HBV) and human immunodeficiency virus (HIV). It is structurally similar to lamivudine; it differs only by a fluorine at the 5-position of the nucleic acid. This review focuses on the efficacy and tolerability of FTC in the treatment of chronic hepatitis B, both HBeAg and anti-HBe-positive. Relevant literature was identified through searches of MEDLINE (2001-January 2008). The review of literature suggests that the role of emtricitabine as monotherapy may be limited by its structural similarity to lamivudine and the corresponding risk of development of drug resistance; however, some studies seem to evidence an efficacy for emtricitabine in association with other antiviral drugs, as adefovir dipivoxil and clevudine. Other studies are needed to evaluate the efficacy of this new drug in particular in association with other antiviral drugs.
Keywords: **Emtricitabine, Hepatitis B, Adverse Events, Therapeutic Use**

Introduction

Chronic hepatitis B (CHB) infection occurs in approximately 5% of the global population. This infection, if persistent, may lead to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) in 25% to 40% of infected patients and is among the principle 10 causes of death throughout the world [1, 2]. Until recently, the only generally approved treatment for chronic hepatitis B was alpha-interferon, but it has demonstrated moderate efficacy in terms of sustained response (biochemical, virological and histological). In fact, only 20% to 40% of treated patients have responded to therapy, with lower percentages (<10%) among patients infected with precore-mutant strains of hepatitis B virus (HBV) [3, 4]. This form is due to a mutation at nucleotide 1896 in the precore region of the HBV-DNA genome with a stop codon that blocks HBeAg synthesis but still permits HBV replication and hepatitis B core antigen (HBcAg) production, leading to persistence of viremia and persistent or intermittent elevated serum alanine aminotransferase (ALT) levels with frequent evolution of disease into cirrhosis and hepatocellular carcinoma.

The use of nucleotide analogues is a milestone in the treatment of CHB. The FDA of the USA approved the use of lamivudine in adult patients in 1998 and adefovir dipivoxil in 2002. These agents are advantageous for oral administration and safety, but induce a sustained response (after withdrawal of therapy) in only a minority of patients. Thus the treatment should be given in trials in a majority of patients for a long period. In addition, the long-term efficacy of lamivudine is limited by the frequent emergence of drug-resistant HBV mutants [5-7]. Adefovir is associated with a low frequency of resistance but its antiviral effect is not optimal [8, 9]. Entecavir, a cyclopentyl guanosine analog, is a new

**** Correspondence:***
Emilio Palumbo, M.D., Via Dell' Arc. Michele 4, 71100 Foggia, Sondrio, Italy.

Tel/Fax: *+39 881 685 023*

E-mail: *emipalu2003@yahoo.it*

Received: *1 Mar 2008*
Accepted: *10 Jun 2008*

Hep Mon 2008; 8 (2): 125-127

antiviral agent approved by FDA of the USA in March 2005. It is a potent inhibitor of HBV-DNA polymerase and it inhibits both priming and elongation steps of viral DNA replication. It is a selective inhibitor of HBV-DNA and is less effective against lamivudine-resistant mutants than against wild-type HBV effective in combating lamivudine-resistant mutant [10].

Emtricitabine, telbivudine and clevudine are new drugs for HBV-infection. Emtricitabine is a cytosine nucleoside analog with antiviral activity against both HBV and HIV. It is structurally similar to lamivudine; but differs only by a fluorine at the 5-position of the nucleic acid. This review focuses on the efficacy and tolerability of emtricitabine in the treatment of CHB, both HBeAg and anti-HBe positive. Relevant literature was identified through searches of MEDLINE (2001-January 2008). Search terms included emtricitabine, hepatitis B, pharmacology, pharmacokinetics, adverse events, and therapeutic use.

Efficacy and Tolerability

In a recent randomized double-blind study, 98 patients (77 HBeAg-positive and 21 HBeAg-negative) received 25, 100, or 200 mg of emtricitabine once daily for 48 weeks. At 48 weeks, the proportions of patients with undetectable serum HBV-DNA were 3.8%, 42%, and 61% for the 3 doses, respectively. HBeAg loss was observed in a high proportion (40%) of the HBeAg-positive patients (ranging from 32% to 50%, depending on the dose). The results of this study suggested that the optimal dose of emtricitabine is 200 mg once daily. Genotypic analysis made at week 48 showed that 12% of patients treated with 100 mg of emtricitabine and 6% of those treated with 200 mg developed YMDD mutants with drug-resistant HBV. In a subgroup of patients receiving the 200 mg dose for 96 weeks, the resistance rate was 19%. In the 21 anti-HBeAg-negative patients, HBV-DNA loss occurred in a higher proportion (79%) than in HBeAg-positive patients (47%). Overall, ALT levels became normal in 95% of patients at week 48 [11]. These results suggest that emtricitabine has a potent antiviral activity in HBeAg-negative, HBV-DNA-positive patients and it is an active therapeutic agent in this setting. However, the role of emtricitabine as monotherapy may be limited by its structural similarity to lamivudine and the corresponding risk of development of drug resistance.

An oriental study has compared the safety and efficacy of emtricitabine with placebo in patients with HBV. We conducted a randomized (2:1), double-blind study at 34 sites in North America, Asia, and Europe that enrolled adults who had chronic HBV infection but had never been exposed to nucleoside or nucleotide treatment between November 2000 and July 2002. Each patient received either 200 mg of emtricitabine (n=167) or placebo (n=81) once daily for 48 weeks and underwent a pre-treatment and end-of-treatment liver biopsy. At the end of treatment, 103 (62%) of 167 patients receiving active treatment had improved liver histologic findings vs. 20 (25%) of 81 receiving placebo, with significance present in subgroups positive and negative for HBeAg. Serum HBV-DNA readings showed less than 400 copies/mL in 91 (54%) of 167 patients in the emtricitabine group vs. 2 (2%) of 81 in the placebo group; ALT levels were normal in 65% (109/167) vs. 25% (20/81), respectively. At 48 weeks, 20 (13%) of 159 patients in the emtricitabine group with HBV-DNA measured at the end of treatment had detectable virus with resistance mutations. The rate of seroconversion to anti-HBe (12%) and HBeAg loss were not different between arms. The safety profile of emtricitabine during treatment was similar to that of placebo. Post-treatment exacerbation of HBV infection developed in 23% of emtricitabine-treated patients. In patients with chronic HBV, both positive and negative for HBe antigen, 48 weeks of emtricitabine treatment resulted in significant histologic, virologic, and biochemical improvement [12].

The aim of an American study was to evaluate long term safety and antiviral activity of different doses of emtricitabine given once daily to patients chronically infected with hepatitis B. Eligible patients were randomized in a double-blind, parallel study to evaluate 25, 100 or 200 mg once daily doses of emtricitabine for 48 weeks. Patients were then followed for an additional 48 weeks on open-label 200 mg emtricitabine. Emtricitabine was well tolerated and produced a dose-dependent antiviral response. After 2 years, 53% of the patients had serum HBV-DNA negative, 33% seroconverted to anti-HBe and 85% had normal ALT. Eighteen percent of the patients who had received 200 mg emtricitabine for 2 years developed resistance mutations [13]. The aim of a recent study was to determine the efficacy of adefovir dipivoxil (ADV) plus emtricitabine combination therapy in chronic HBV infection vs. ADV monotherapy. Thirty treatment-naive, HBeAg-positive patients were randomized to either a combination of ADV plus emtricitabine (n=14) or ADV plus placebo monotherapy (n=16) for 96 weeks. HBV-DNA was measured by polymerase chain reaction. Treatment was stopped in those with HBeAg seroconversion.

The median decrease in HBV-DNA at week 96 was higher in the combination group (-5.30 vs. -3.98 log_{10} copies/ml). More patients in the combination group had normalization of ALT and HBV-DNA< 300 copies/ml at week 96 when compared with the monotherapy group [11 of the 14 patients (78.6%) vs. 6 of the 16 patients (37.5%)]. HBeAg seroconversion at week 96 was similar in the 2 groups [2/14 (14.3%) vs. 4/16 (25.0%)]. No ADV or emtricitabine resistance was detected at week 96. In those with HBeAg seroconversion, 50.0% had post-treatment relapse. This study suggest that the combination of ADV plus emtricitabine results in more potent suppression of HBV-DNA over 96 weeks of therapy [14].

Another experience summarizes the results of a double-blind, multicenter study of patients with CHB who had completed a 3-phase study on FTC and were randomized 1:1 to 200 mg emtricitabine once daily (QD) plus 10 mg CLV QD or 200 mg emtricitabine QD plus placebo for 24 weeks with 24 weeks of follow-up. One hundred and sixty-three patients were treated (82 with emtricitabine plus CLV [emtricitabine+CLV] and 81 with FTC), after 24 weeks of treatment, 74% (emtricitabine+CLV) vs. 65% (FTC alone) had serum HBV-DNA levels of < 4,700 copies/ml (P=0.114). Twenty-four weeks post-treatment, the mean change in serum HBV-DNA levels from baseline was -1.25 log10 copies/ml (emtricitabine+CLV), 40% had undetectable viremia (vs. 23% for emtricitabine alone), and 63% had normal ALT levels (vs. 42% for emtricitabine alone). Therefore in this study after 24 weeks of treatment no significant difference was observed between the arms, but there was a significantly greater virologic and biochemical response at 24 weeks post-treatment in the emtricitabine+CLV arm [15].

Conclusion

Emtricitabine is a cytosine nucleoside analog with antiviral activity against both HBV and HIV. It is structurally similar to lamivudine; but differs only by a fluorine at the 5-position of the nucleic acid. The role of emtricitabine as monotherapy may be limited by its structural similarity to lamivudine and the corresponding risk of development of drug resistance. Some studies seem to evidence an efficacy for emtricitabine in association with other antiviral drugs, as ADV and clevudine. Other studies are needed to evaluate the efficacy of this new drug in particular in association with other antiviral drugs.

References

1. Chu CM, Liaw YF. Natural history of chronic hepatitis B virus infection: an immunopathological study. *J Gastroenterol Hepatol* 1997; **12**: S218-22.
2. Ganem D, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med* 2004; **350**: 1118-29.
3. Oliveri F, Santantonio T, Bellati G, Colombatto P, Mels GC, Carriero L, *et al.* Long term response to therapy of chronic anti-HBe-positive hepatitis B is poor independent of type and schedule of interferon. *Am J Gastroenterol* 1999; **94**: 1366-72.
4. van Zonneveld M, Honkoop P, Hansen BE, Niesters HG, Murad SD, de Man RA, *et al.* Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. *Hepatology* 2004; **39**: 804-10.
5. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, *et al.* A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med* 1998; **339**: 61-8.
6. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, *et al.* Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999; **341**: 1256-63.
7. Lau DT, Khokhar MF, Doo E, Ghany MG, Herion D, Park Y, *et al.* Long-term therapy of chronic hepatitis B with lamivudine. *Hepatology* 2000; **32**: 828-34.
8. Zeng M, Mao Y, Yao G, Wang H, Hou J, Wang Y, et al. A double-blind randomized trial of adefovir dipivoxil in Chinese subjects with HBeAg-positive chronic hepatitis B. *Hepatology* 2006; **44**: 108-16.
9. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; **348**: 800-7.
10. Yan JH, Bifano M, Olsen S, Smith RA, Zhang D, Grasela DM, *et al.* Entecavir pharmacokinetics, safety, and tolerability after multiple ascending doses in healthy subjects. *J Clin Pharmacol* 2006; **46**: 1250-8.
11. Leung N, Gish RG, Wang C. A randomized, double-blind, comparison of 3 doses of emtricitabine (FTC) in patients with chronic hepatitis B (CHB) given 48 weeks of treatment (FTCB-102). *Hepatology* 2001; **34**: 349A.
12. Lim SG, Ng TM, Kung N, Krastev Z, Volfova M, Husa P, *et al.* A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B. *Arch Intern Med* 2006; **166**: 49-56.
13. Gish RG, Trinh H, Leung N, Chan FK, Fried MW, Wright TL, *et al.* Safety and antiviral activity of emtricitabine (FTC) for the treatment of chronic hepatitis B infection: a two-year study. *J Hepatol* 2005; **43**: 60-6.
14. Hui CK, Zhang HY, Bowden S, Locarnini S, Luk JM, Leung KW, *et al.* 96 weeks combination of adefovir dipivoxil plus emtricitabine vs. adefovir dipivoxil monotherapy in the treatment of chronic hepatitis B. *J Hepatol* 2008; **48**: 714-20.
15. Lim SG, Krastev Z, Ng TM, Mechkov G, Kotzev IA, Chan S, *et al.* Randomized, double-blind study of emtricitabine (FTC) plus clevudine versus FTC alone in treatment of chronic hepatitis B. *Antimicrob Agents Chemother* 2006; **50**: 1642-8.