Combination treatment in HBeAg-negative chronic hepatitis B

Konstantinos Tziomalos

Abstract

Chronic hepatitis B (CHB) represents an important public health problem. HBeAg-negative CHB is frequently associated with advanced liver disease and its prevalence is increasing. Monotherapy with either interferon (conventional or pegylated) or nucleoside/nucleotide analogues has its limitations. It has been suggested that a combination of these agents might increase antiviral efficacy. However, existing data do not support this hypothesis, even though combination treatment appears to reduce the risk for emergence of lamivudine resistance. Nevertheless, most existing combination studies are small, and it is possible that they have not been designed to detect significant differences between combination treatment and monotherapies. Another limitation of these studies is that, in most of them, lamivudine treatment was discontinued after 1 year, a strategy that is not followed in clinical practice. It was thought to be interesting to evaluate the combination of a short course of interferon (particularly pegylated) with the long-term administration of nucleotide or nucleoside analogues. The efficacy of combining pegylated interferon with the newer nucleotide or nucleoside analogues or of nucleotide with nucleoside analogues could also be evaluated. However, findings show that until more data are available, combination therapy cannot be recommended as first-line treatment in patients with CHB. On the other hand, addition of therapy with adefovir or tenofovir is the treatment of choice in patients who develop resistance to lamivudine. In patients with cirrhosis, a combination of lamivudine/adefovir may also be used as initial treatment; another option would be to add tenofovir in patients with an insufficient response to entecavir.

Key words: Interferon; Lamivudine; Adefovir; Telbivudine; Entecavir; Tenofovir; Combination; Monotherapy; HBeAg negative chronic hepatitis B; Resistance

INTRODUCTION

Chronic hepatitis B (CHB) represents an important public health problem\(^1\). It is estimated that 350 million people worldwide are affected by CHB, and 500,000 to 1.2 million patients die each year of the complications (mainly cirrhosis and hepatocellular carcinoma) of CHB\(^1\). HBeAg-negative CHB is characterized by the presence of the hepatitis B virus (HBV) with mutations in the precore or basic core promoter region, which prevent the synthesis of HBeAg\(^2\). The prevalence of HBeAg-negative CHB appears to be increasing; median rates are 33% in Europe (range: 10-72), 14% in the United States (range: 13-22) and 15% in Asia (range: 5-47)\(^3\). Patients with HBeAg-negative CHB are more likely to have severe liver disease at the time of diagnosis, and to progress to cirrhosis than patients with...
HBeAg-positive CHB\[2\]. The management of HBeAg-negative CHB is therefore an important aspect of the treatment of CHB.

**LIMITATIONS OF MONOTHERAPY IN CHB**

Seven agents are currently approved for the treatment of CHB, including interferon [conventional interferon (IFN) and pegylated (PEG) IFN α-2a] and the nucleoside/nucleotide analogues [lamivudine (LAM), adefovir (ADV), telbivudine, entecavir and tenofovir][4,5]. IFN stimulates cell-mediated immune responses against HBV, whereas the nucleoside/nucleotide analogues inhibit HBV replication by acting on the HBV polymerase[6]. The advantage of IFN is that it is administered for a defined period (16-48 wk), induces sustained responses in some patients and is not associated with the development of HBV resistance[4,5]. However, IFN treatment requires subcutaneous injections and is frequent associated with side effects[6]. The nucleoside/nucleotide analogues are given orally and are well tolerated[4,5]. However, stopping these agents leads to a rebound of HBV replication in most cases and they therefore have to be given for long periods of time and probably indefinitely[4,5]. Unfortunately this strategy is compromised by the development of HBV resistance[4,5].

**CONVENTIONAL IFN PLUS LAM COMBINATION**

It is clear that monotherapy with either IFN or nucleoside/nucleotide analogues has limitations. Since these agents have different mechanisms of action, it has been suggested that combining them might result in more potent and sustained suppression of viral replication[4,5]. This in turn also reduce the risk for development of antiviral resistance[7]. Accordingly, several studies compared IFN/LAM combination with LAM monotherapy in patients with HBeAg-negative CHB[8-12]. End-of-treatment virological and biochemical response rates with the 2 treatments were either similar[9,13] or higher with IFN/LAM combination[8,11,13]. However, sustained (i.e. after treatment discontinuation) virological and biochemical response rates were similar with IFN/LAM combination and LAM monotherapy in all studies[8,10,12]. Moreover, improvement in liver histology was either similar in the 2 groups[12] or greater with LAM monotherapy[9,10]. Development of LAM-resistant mutants was found to be more frequent in patients treated with LAM monotherapy in some[8,11,13] but not all studies[9,10,12]. Treatment discontinuation rates were similar in the 2 groups[8,11,12]. Interestingly, the administration of higher doses of IFN (up to 10 MU tiw), or for longer periods (up to 24 mo) was not associated with better results of IFN/LAM combination[8,12].

**PEG-IFN PLUS LAM COMBINATION**

Pegylated IFN appears to be more effective than conventional IFN and has a more convenient dosing scheme (one weekly administration tiw with conventional IFN)[9]. A limited number of studies have evaluated the effectiveness of a PEG-IFN/LAM combination compared with LAM monotherapy in patients with HBeAg-negative CHB[11-13]. In the largest study, Marcellin et al[13] randomly assigned 537 patients to 48 wk of treatment with a PEG-IFN α-2a/LAM combination, PEG-IFN α-2a monotherapy or LAM monotherapy. After a follow-up time of 24 wk after discontinuing treatment, those patients treated with the PEG-IFN α-2a/LAM combination showed higher virological and biochemical response rates than those treated with LAM monotherapy[13]. However, response rates were similar in the PEG-IFN α-2a/LAM combination and PEG-IFN α-2a monotherapy patient groups[13]. Moreover, rates of histological response were similar in the 3 groups[13]. The rates of adverse events were similar in the PEG-IFN α-2a/LAM combination and PEG-IFN α-2a monotherapy groups but significantly lower in the LAM monotherapy group[13]. Treatment with PEG-IFN α-2a/LAM combination was associated with lower rates of emergence of LAM resistance compared with LAM monotherapy[13]. In 2 smaller studies (n = 48 and n = 126, respectively PEG-IFN α-2b/LAM combination and PEG-IFN α-2b monotherapy administered for 48 wk resulted in similar end-of-treatment and sustained biochemical and virological response rates 24 wk later[4,13]. Liver biopsy was not performed nor were rates of emergence of LAM resistance reported in the latter studies[4,13].

**STAGGERED IFN/LAM COMBINATION**

In *vitro* studies have suggested that LAM restores HBV-specific cytotoxic T lymphocyte reactivity[16,17]. It was therefore hypothesized that LAM pre-treatment might increase responsiveness to subsequent IFN administration[16,17]. Accordingly, a number of studies have evaluated a staggered treatment scheme, with 1-6 mo of LAM monotherapy preceding treatment with 1-12 mo of a IFN/LAM combination[12,18-21]. In some studies, the IFN/LAM combination was followed by 6 mo of LAM monotherapy[19] or 6 mo of IFN monotherapy[18,20]. The IFN/LAM combination was compared with LAM monotherapy[12,22], IFN monotherapy[18] or both[19]. End-of-treatment virological and biochemical response rates were similar in the IFN/LAM combination and LAM monotherapy groups[12,18-21] and higher than those of the IFN monotherapy groups[18,19]. In most studies, after 6-27 mo of follow-up, sustained virological and biochemical response rates were also similar in the IFN/LAM combination and the LAM monotherapy[12,18,21] or IFN monotherapy groups[18,19]. The biochemical response rates were higher in the IFN/LAM combination group at 24 wk after treatment discontinuation in only one study, but virological response rates did not differ
SEROCONVERSION TO ANTI-HBS WITH COMBINATION TREATMENT

Loss of HBsAg and seroconversion to antiHBs indicates resolution of CHB and is considered as a complete response to treatment. However, this result is rarely achieved with monotherapy with either IFN or nucleoside/nucleotide analogues. Some uncontrolled studies suggested that IFN combined with either LAM or ADV is associated with high rates of seroconversion to antiHBs. However, in the controlled studies there were no differences in rates of HBsAg loss or seroconversion to antiHBs between IFN (conventional or PEG-IFN) and LAM combination (either synchronous or sequential) and either monotherapy. A limited number of studies have assessed the effects of combining nucleotide and nucleoside analogues in patients with HBeAg-positive CHB. The use of ADV, combined with either LAM or emtricitabine (which is not yet approved in CHB) was shown to reduce HBV DNA levels more than ADV monotherapy. In contrast, combining telbivudine and LAM (i.e. 2 nucleotide analogues) was not shown to be more effective than telbivudine monotherapy. In the only study which evaluated the combination of oral antiviral agents in patients with HBeAg-negative CHB, 163 patients with CHB (48% HBeAg-negative) were treated with a combination of emtricitabine plus clevudine or emtricitabine monotherapy. Neither of these agents is yet approved in CHB. At the end of the 24-wk treatment period, virological and biochemical response rates were similar in the 2 groups. However, 24 wk after treatment discontinuation, virological and biochemical response rates were higher in the emtricitabine/clevudine combination group. Emtricitabine-resistant mutants emerged at the same rate in the 2 groups. Adverse events were similar in the 2 groups but post-treatment exacerbation of CHB occurred less frequently in the emtricitabine/clevudine combination group. In a study recently presented in abstract form, a tenofovir/emtricitabine combination was shown not to be more effective than tenofovir monotherapy in patients with persistent viral replication, despite treatment with ADV (n = 105, 27% HBeAg-negative).

CONCLUSION

In conclusion, available data do not support the hypothesis that combination treatment improves virological or biochemical response rates compared with monotherapy in HBeAg-negative CHB. Combination treatment might also reduce compliance and increase the cost of therapy, as well as the risk of incurring side effects and drug interactions. On the other hand, the advantage of combination treatment is that it appears to reduce the risk for development of LAM resistance. However, most studies are small and it is possible that they were not designed to detect significant differences between a IFN/LAM combination and LAM monotherapy. In addition, the inclusion of non-responders to previous IFN treatment might have also reduced the efficacy of the IFN/LAM combination. Another limitation of these studies is that LAM treatment was discontinued after 1 year in most of them, a strategy that is not normally followed in clinical practice. It would be interesting to evaluate the combination of a short course of IFN (particularly PEG-IFN) with long-term administration of nucleotide or nucleoside analogues. The efficacy of combining PEG-IFN with the newer nucleotide or nucleoside analogues or of nucleotide with nucleoside analogues should also be evaluated. Until more data are available, combination therapy cannot be recommended as first-line treatment in patients with CHB. However, combination therapy is the treatment of choice in patients who develop resist-

significantly between the 2 groups. LAM resistance was observed more frequently in the LAM monotherapy group, but not all studies. Improvement in liver histology was similar with the IFN/LAM combination and LAM monotherapy, but less with IFN monotherapy. Treatment discontinuation rates were similar with the IFN/LAM combination and LAM monotherapy. Only 1 study evaluated a staggered combination scheme including PEG-IFN in patients with HBeAg-negative CHB. In this report, 18 patients were treated with a LAM/PEG-IFN α-2b combination (5 mo LAM, 3 mo LAM/PEG-IFN α-2b and 9 mo PEG-IFN α-2b alone) and 24 patients were treated with LAM alone for a median of 25 mo. At the end of the treatment, virological and biochemical response rates did not differ significantly between groups. At 12 mo after treatment discontinuation, virological response rates did not differ significantly between the 2 groups but biochemical response rates were higher in the LAM/PEG-IFN α-2b combination group. LAM resistance was observed more frequently in the LAM monotherapy group. Finally, only 1 study compared a staggered combination scheme (12 wk of LAM monotherapy followed by 40 wk of an IFN/LAM combination) with a IFN/LAM combination for 52 wk. This study also included a group treated with LAM monotherapy for 52 wk. End-of-treatment and end-of-follow-up virological and biochemical response rates, changes in liver histology and rates of development of LAM-resistant mutants were similar in the 3 groups.

COMBINATION TREATMENT WITH DIFFERENT NUCLEOSIDE AND NUCLEOTIDE ANALOGUES

Combination treatment with a nucleotide analogue (lamivudine or telbivudine) and a nucleoside analogue (e.g. adeovir or tenofovir) might be a therapeutic option because these agents have different resistance profiles. A limited number of studies have assessed the effects of combining nucleotide and nucleoside analogues in patients with HBeAg-positive CHB. The use of ADV, combined with either LAM or emtricitabine (which is not yet approved in CHB) was shown to reduce HBV DNA levels more than ADV monotherapy. In contrast, combining telbivudine and LAM (i.e. 2 nucleotide analogues) was not shown to be more effective than telbivudine monotherapy. In the only study which evaluated the combination of oral antiviral agents in patients with HBeAg-negative CHB, 163 patients with CHB (48% HBeAg-negative) were treated with a combination of emtricitabine plus clevudine or emtricitabine monotherapy. Neither of these agents is yet approved in CHB. At the end of the 24-wk treatment period, virological and biochemical response rates were similar in the 2 groups. However, 24 wk after treatment discontinuation, virological and biochemical response rates were higher in the emtricitabine/clevudine combination group. Emtricitabine-resistant mutants emerged at the same rate in the 2 groups. Adverse events were similar in the 2 groups but post-treatment exacerbation of CHB occurred less frequently in the emtricitabine/clevudine combination group. In a study recently presented in abstract form, a tenofovir/emtricitabine combination was shown not to be more effective than tenofovir monotherapy in patients with persistent viral replication, despite treatment with ADV (n = 105, 27% HBeAg-negative).
Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; 11: 97-107

2. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008; 48: 335-352

3. Funk ML, Rosenberg DM, Lok AS. World-wide epidemiology of HBsAg-negative chronic hepatitis B and associated precore and core promoter variants. *J Viral Hepat* 2002; 9: 52-61

4. Sorrell MF, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, Kern ER, McHugh JA, Petersen GM, Rein MF, Strader DB, Trotter HT. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. *Ann Intern Med* 2009; 150: 104-110

5. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007; 45: 507-539

6. Zoulim F, Perrillo R. Hepatitis B: reflections on the current approach to antiviral therapy. *J Hepatol* 2008; 48: Suppl 1: S2-S19

7. Terrault NA. Benefits and risks of combination therapy for hepatitis B. *Hepatology* 2009; 49: S122-S128

8. Santantonio T, Niro GA, Sinisi E, Leandro G, Insalata M, Guastadisegni A, Facciorusso D, Gravinese E, Andriulli A, Pastore G. Lamivudine/interferon combination therapy in anti-HBe positive chronic hepatitis B patients: a controlled pilot study. *J Hepatol* 2002; 36: 799-804

9. Akara US, Ersoz G, Gursan F, Karasu Z, Saritas E, Yuce G, Batur Y. Interferon-lamivudine combination is no better than lamivudine alone in anti-HBe-positive chronic hepatitis B. *Antivir Ther* 2004; 9: 325-334

10. Akyuz F, Kaymakoglu S, Demir K, Aksoy N, Karaca C, Danaligoglu A, Onel D, Badur S, Besisik F, Cakaloglu Y, Okten A. Lamivudine monotherapy and lamivudine plus interferon alpha combination therapy in HBsAg negative chronic hepatitis B not responding to previous interferon alpha monotherapy. *Acta Gastroenterol Belg* 2007; 70: 20-24

11. Economou M, Manolakopoulos S, Trikalinos TA, Filis S, Bethanis S, Tzourmakliotis D, Avgerinos A, Raptis S, Tsiakas E. Interferon-alpha plus lamivudine vs lamivudine reduces breakthroughs, but does not affect sustained response in HBsAg-negative chronic hepatitis B. *World J Gastroenterol* 2005; 11: 5882-5887

12. Scotto G, Palombo E, Fazio V, Cibelli DC, Saracino A, Angarano G. Efficacy and tolerability of lamivudine alone versus lamivudine plus alpha-interferon for treatment of chronic active hepatitis B in patients with a precore-mutant variant. *Infec Med* 2006; 14: 145-151

13. Marelli P, Lai JY, Bonino F, Farci P, Hadziyannis S, Jin R, Lu ZM, Piratvisuth T, Germanidis G, Yurdakul C, Diaco M, Gurel S, Fan JY, Button P, Pluck N. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBsAg-negative chronic hepatitis B. *N Engl J Med* 2004; 351: 1206-1217

14. Kaymakoglu S, Ozgu D, Gur G, Gurel S, Tankurt E, Ersoz G, Ozenirler S, Kalayci C, Poturoglu S, Cakaloglu Y, Okten A. Pegylated interferon Alfa-2b monotherapy and pegylated interferon Alfa-2b plus lamivudine combination therapy for patients with hepatitis B virus E antigen-negative chronic hepatitis B. *Antimicrob Agents Chemother* 2007; 51: 3020-3022

15. Papadopoulos VP, Chrysagis DN, Protapouss AN, Goulis IG, Dimitriadis GT, Mimitidis KP. Peginterferon alfa-2b as monotherapy or in combination with lamivudine in patients with HBsAg-negative chronic hepatitis B: a randomised study. *Med Sci Monit* 2009; 15: CR56-CR61

16. Boni C, Bertoletti A, Penna A, Cavalli A, Pili M, Urbani S, Scognamiglio P, Boehme R, Panebianco R, Faccadori F, Ferrari C. Lamivudine treatment can restore T cell responsiveness in chronic hepatitis B. *J Clin Invest* 1998; 102: 968-975

17. Boni C, Penna A, Oggi GS, Bertoletti A, Pili M, Cavallo C, Cavalli A, Urbani S, Boehme R, Panebianco R, Faccadori F, Ferrari C. Lamivudine treatment can overcome cytotoxic T-cell hyporesponsiveness in chronic hepatitis B: new perspectives for immune therapy. *Hepatology* 2001; 33: 963-971

18. Manesis EK, Papatheodoridis GV, Hadziyannis SJ. A partially overlapping treatment course with lamivudine and interferon in hepatitis B e antigen-negative chronic hepatitis B. *Aliment Pharmacol Ther* 2006; 23: 99-106

19. Jabali MF, Fabbi C, Liva S, Azzarelli F, Nigro G, Giovanelli S, Ferrara F, Miracolo A, Marchetto S, Montagnani M, Colecchia A, Festi D, Reggiani LB, Rode E, Mazzella G. Long-term alpha interferon and lamivudine combination therapy in non-responders patients with anti-HBe-positive chronic hepatitis B: results of an open, controlled trial. *World J Gastroenterol* 2003; 9: 1491-1495

20. Shi M, Wang RS, Zhang H, Zhu YF, Han B, Zhang Y, Jin LJ, Yang JZ, Xu YP. Sequential treatment with lamivudine and interferon-alpha monotherapies in hepatitis B e antigen-negative Chinese patients and its suppression of lamivudine-resistant mutations. *J Antimicrob Chemother* 2006; 58: 1031-1035

21. Yurdakul C, Bozkaya H, Cetinkaya H, Sahin T, Karaoguz D, Toruner M, Erkan O, Heper AO, Erden E, Bozdayi AM, Uzunalinoglu O. Lamivudine vs lamivudine and interferon combination treatment of HBeAg(-) chronic hepatitis B. *J Viral Hepat* 2005; 12: 262-268

22. Vassilaidis T, Tziomalos K, Petsaoura K, Zagriss T, Giouleme O, Soulteris K, Grammatikos N, Theodoropoulos K, Mpoumponaris A, Dona K, Zevos P, Nikolaidis N, Orfanou-Koumerkeridou E, Balaska A, Eugenidis N. Lamivudine/pegylated interferon alfa-2b sequential combination therapy compared with lamivudine monotherapy in HBsAg-negative chronic hepatitis B. *J Viral Hepat* 2007; 22: 1582-1588

23. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 2007; 45: 1056-1075

24. Nikolaidis NL, Giouleme OI, Tziomalos KA, Saveriadis AS, Grammatikos N, Doukelis P, Voutsas AD, Vassilaidis T, Petsaoura K, Orfanou-Koumerkeridou E, Balaska A, Eugenidis NP. Interferon-long term lamivudine combination therapy in anti-HBe positive chronic hepatitis B patients. *J Gastroenterol Hepatol* 2005; 20: 1721-1725

25. Wursthorn K, Lutgehetmann M, Dandi M, Volz T, Buggisch P, Zoller B, Longerich T, Schirmacher P. Peginterferon alfa-2b plus adefovir induce strong cccDNA and partially overlapping treatment course with lamivudine and interferon in hepatitis B e antigen-negative chronic hepatitis B. *Antimicrob Agents Chemother* 2007; 51: 3020-3022

26. Lai CL, Yuen MF. Chronic hepatitis B--new goals, new treatment. *N Engl J Med* 2008; 359: 2488-2491

27. Sung JJ, Lai JY, Zheng S, Chow WC, Heathcote EJ, Perrillo RP, Brosgart CL, Woessner MA, Scott SA, Gray DF, Gardner SD. Lamivudine compared with lamivudine and adefovir dipivoxil for the treatment of HBsAg-positive chronic hepatitis B. *J Hepatol* 2008; 49: 728-735
Hui CK, Zhang HY, Bowden S, Locarnini S, Luk JM, Leung KW, Yueng YH, Wong A, Rousseau F, Yuen KY, Naoumov NN, Lau GK. 96 weeks combination of adefovir dipivoxil plus emtricitabine vs. adefovir dipivoxil monotherapy in the treatment of chronic hepatitis B. *J Hepatol* 2008; 48: 714-720

Lai CL, Leung N, Teo EK, Wong F, Hann HW, Han S, Poynard T, Myers M, Chao G, Lloyd D, Brown NA. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology* 2005; 129: 528-536

Lim SG, Krastev Z, Ng TM, Mechkov G, Kotzev IA, Chan S, Mondou E, Snow A, Sorbel J, Rousseau F. Randomized, double-blind study of emtricitabine (FTC) plus clevudine versus FTC alone in treatment of chronic hepatitis B. *Antimicrob Agents Chemother* 2006; 50: 1642-1648

Berg T, Moller B, Trinh H, Chan S, Marcellin P, Suarez E, Snow-Lampart A, Oldach D, Sorbel J, Borroto-Esoda K, Frederick D, Rousseau F. Tenofovir disoproxil fumarate (TDF) versus emtricitabine plus TDF (FTC/TDF) for treatment of chronic hepatitis B (CHB) in patients with persistent viral replication receiving adefovir dipivoxil. *J Hepatol* 2009; 50: S328

S- Editor Zhang HN  L- Editor Herholdt A  E- Editor Ma WH