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Comparison of the efficacy of thymosin alpha-1 and interferon alpha in the treatment of chronic hepatitis B: A meta-analysis

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Abstract

Chronic hepatitis B virus (HBV) infection is a serious problem because of its worldwide distribution and possible adverse sequelae, such as cirrhosis and hepatocellular carcinoma. Thymosin alpha-1 (Tα1) is an immune modifier that has been shown to be effective for chronic hepatitis B (CHB) in some trials. But the trials comparing Tα1 vs. interferon alpha (IFNα) treatment in CHB have been small and the results have been inconsistent. So we conducted a meta-analysis to compare the efficacy of Tα1 and IFNα in the treatment of CHB. Generally, four randomized controlled trials including 199 CHB patients who received Tα1 or IFNα treatment were identified through MEDLINE and EMBASE online search. Virological (for hepatitis B e antigen (HBeAg) positive patients, loss of HBV DNA and HBeAg; for HBeAg negative patients, loss of HBV DNA), biochemical (normalization of transaminases) and complete responses (fulfill criteria of biochemical and virological response simultaneously) were analyzed using the intention-to-treat method. The odds ratio (OR) was used to measure the magnitude of the efficacy. The ORs (95% confidence interval) of the virological response, biochemical response and complete response of Tα1 over IFNα at the end of 6 months treatment were 0.62 (0.35, 1.10), 0.60 (0.34, 1.05) and 0.54 (0.30, 0.97), respectively. The ORs (95% confidence interval) of the virological response, biochemical response and complete response of Tα1 over IFNα at the end of follow-up (6 months post-treatment) were 3.71 (2.05, 6.71), 3.12 (1.74, 5.62) and 2.69 (1.47, 4.91), respectively. These data showed that compared with IFNα, the benefit of Tα1 was not immediately significant at the end of therapy, but virological, biochemical and complete response had a tendency to increase or accumulate gradually after the therapy. For three of the four trials that studied HBeAg-negative patients, the results are mostly applicable to HBeAg-negative CHB.

Keywords: Thymosin; Interferon; Hepatitis B; Meta-analysis

1. Introduction

Hepatitis B virus (HBV) infection is a global public health problem as it is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) with up to one million HBV carriers dying of HBV associated liver disease annually (Safioleas et al., 2007). Several major advances in the treatment of chronic hepatitis B have been made over the last several years. Currently, interferon alpha (IFNα) and four nucleoside analogue (NA): lamivudine, adefovir dipivoxil, entecavir, and most recently, telbivudine have been approved for the treatment of chronic hepatitis B (Lok and McMahon, 2007).

IFNα has reasonably good efficacy with initial response rates of 30–40% compared with 10–20% among untreated controls. However, of those who responded to IFNα therapy, 56% relapsed within the first year after discontinuation of therapy (median 3.1 months) (Manesis and Hadziyannis, 2001). In addition, IFNα has a poor side-effect profile, leading to inadequate compliance and frequent need for dose reduction (Manesis and Hadziyannis, 2001; Liaw, 2002). Once-daily nucleoside analogue rapidly produces a suppression of HBV DNA replication. However, most of patients relapse once therapy is stopped (Lok and McMahon, 2007).

Thymosin alpha-1 (Tα1) is an immunemodulating peptide that has been shown to enhance Th1 cytokine production as well as T-cell differentiation and maturation (Rasi et al., 2003). Tα1 therapy is used in many countries worldwide for the treatment of chronic hepatitis B. Several clinical studies have shown

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that treatment with Tα1 monotherapy results in significantly higher sustained response rates when compared with controls and exhibits no significant side effects. Moreover, complete virological response tends to increase or accumulate gradually after the cessation of Tα1 therapy (Zavaglia et al., 2000; Mutchnick et al., 1999, 1991; Chien et al., 1998). A meta-analysis conducted by Chan et al. (2001) has shown that compared with no treatment, thymosin is effective in suppressing viral replication in chronic HBV infection. And recently, some randomized controlled clinical trials compared the efficacy of Tα1 and IFNα in the treatment of chronic hepatitis B. Thus, we conducted this meta-analysis of these trials to assess the evidence obtained on the efficacy of Tα1 treatment in chronic HBV infection.

2. Methods

2.1. Literature search and data extraction

All English articles were retrieved by using searches of MEDLINE and EMBASE. Included terms were *thymosin* and *hepatitis B* or *HBV*. Our search was limited to human studies. All articles were identified by a search from 1966 to August 2007. Additional studies were identified by scrutiny of the reference lists of trial publications and review articles and by writing to principal investigators of identified eligible trials. The selection of papers and data extraction using the same data extraction form was conducted independently by two investigators. Basic information obtained from each eligible trial included the number of patients randomized into each compared group at the outset of the trial, the treatment regime, duration of follow-up and the treatment outcomes at the end of treatment and/or during the post-treatment follow-up period. Articles were examined to eliminate duplicate reports of the same trial, and uncertainties in the data were clarified by contacting the principal investigators through writing when necessary.

2.2. Inclusion and exclusion criteria

Prospective, randomized controlled trials comparing Tα1 vs. IFNα in the treatment of chronic hepatitis B were considered for analysis. Patients were HBV DNA-positive and had elevated alaninetransaminase (ALT) levels. Studies were included in the meta-analysis if they had a minimum treatment duration of 24 weeks and reported end-of-treatment and/or sustained (more than 6 months post-treatment) virological, biochemical and/or complete responses. Trials including patients suffering from other forms of viral hepatitis (hepatitis C or hepatitis D) or receiving antiviral drugs other than Tα1and IFNα were excluded.

2.3. Excluded and included trials

Eleven potentially eligible randomized trials using Tα1 in the treatment of chronic HBV infection were identified (Zavaglia et al., 2000; Mutchnick et al., 1999, 1991; Chien et al., 1998, 2006; Iino et al., 2005; Andreone et al., 1996; Zhuang et al., 2001; You et al., 2001, 2005, 2006). Five comparing Tα1 vs. no treatment or placebo (Zavaglia et al., 2000; Mutchnick et al., 1999, 1991; Chien et al., 1998, 2006) and one comparing different dose of Tα1 (Iino et al., 2005) were excluded. Among other five randomized trials comparing Tα1 vs. IFNα (Andreone et al., 1996; Zhuang et al., 2001; You et al., 2001, 2005, 2006), one duplicate publication was excluded (You et al., 2001).

2.4. Definition of main outcomes

Virological response was defined as the disappearance of HBV DNA in the serum plus the loss of hepatitis B e antigen (HBeAg) if the patients were HBeAg-positive before treatment and the disappearance of HBV DNA if the patients were HBeAg-negative before treatment. Biochemical response was defined as the normalization of the ALT levels. Complete response was defined as fulfilling criteria of biochemical and virological response simultaneously. We analyzed the outcome at the end of treatment and at the end of follow-up (6 months post-treatment).

2.5. Statistical analysis

Virological, biochemical and complete responses were analyzed separately using the intention-to-treat method. We used the ratio of the odds of the main outcomes in the Tα1-treated group over that in the IFNα-treated group as the measure of efficacy. The 95% confidence interval (CI) for the combined odds ratio (OR) is also provided. Meta-analysis was performed using fixed-effect or random-effect methods, depending on absence or presence of significant heterogeneity (DerSimonian and Laird, 1986). Statistical heterogeneity between trials was evaluated by the Cochran χ^2 test and was considered to exist when $P < 0.10$. In the absence of statistically significant heterogeneity, the fixed-effect method was used to combine the results. When the heterogeneity test was statistically significant ($P = 0.10$ or lower), the random-effect method was used. The combined result was an average OR and 95% CI weighted according to the standard error of the OR of the trial, $P < 0.05$ was considered statistically significant. We used funnel plots (i.e. plots of study results against precision) to assess publication bias, and tested the symmetry of the funnel plot using Egger's test (Egger et al., 1997; Sterne and Egger, 2001). Analyses were performed with STATA version 9.0 (Stata Corp, College Station, Tx) and Review Manager version 4.2 (RevMan, The Cochrane Collaboration, Oxford, England).

3. Results

3.1. Description of the included trials

Table 1 shows the characteristics of the four trials included in the meta-analysis, with a total of 199 patients. All patients were anti-HBV treated naïve. At entry, all patients with presence of hepatitis B surface antigen (HBsAg) in serum for at least 12 months, positive serum tests for HBV DNA (one trial by liquid hybridization (Andreone et al., 1996) and the other three trials by polymerase chain reaction (Zhuang et al., 2001; You et al., 2005, 2006)) documented on at least two occasions and at least 3 months apart during the 12 months before entry,