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EXPERT OPINION

Thymosin alpha-1 treatment in chronic hepatitis B

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Introduction: Stimulating a successful host immune response may be a promising helpful therapy to achieve elimination of hepatitis B virus (HBV) infection in chronic hepatitis B (CHB). Thymosin α-1 (Tα-1), as an immunomodulatory agent, can enhance T-cell response in CHB patients and has been widely studied either alone or in combination with nucleos(t)ide analogs. This editorial reviews these articles to present the efficacy of Tα-1 in CHB.

Areas covered: English and Chinese articles in MEDLINE, EMBASE, the Cochrane Controlled Trial Registry, Chinese periodical full-text database of science and technology, Chinese periodical full-text database and Wan-fang database by thesis search were collected and reviewed.

Expert opinion: In CHB, Tα-1monotherapy is effective in suppressing viral replication compared with untreated control or conventional interferon. Most of the combination therapy of Tα-1 plus either lamivudine or IFN-α showed better effects on HBV DNA suppression and HBeAg seroconversion. Presently, clinical studies of Tα-1 combined with entecavir on the treatment of HBV-cirrhosis are ongoing.

Keywords: hepatitis B, thymosin α-1, treatment

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1. Introduction

Thymosin α-1 (Tα-1) is a highly conserved 28-amino-acid peptide that can enhance immune properties including T-cell maturation and antigen recognition, cytokine modulation and chemokine production, and the activity of natural killer cell-mediated cytotoxicity [1,2]. Recent reports of thymosin clinical applications are in infectious disease (septic shock, acute respiratory distress syndrome, peritonitis, acute cytomegalovirus infection, viral hepatitis B and C), cancer and chemotherapy (lung cancer, melanoma, hepatocellular carcinoma, and breast cancer), and immune deficiency disease patients [3]. In this review we will focus on the effects of Tα-1 as an immunotherapeutic drug on chronic hepatitis B (CHB).

CHB virus (HBV) infection is a dynamic state of interactions between the virus, hepatocytes and the immune system of the host. A vigorous, polyclonal and multispecific cytotoxic (CTL) and T helper cell response to HBV is believed to be responsible for the elimination of the HBV. However, this is usually weak, antigenically restricted or undetectable in patients with chronic HBV infection [4-6]. *In vitro* studies have suggested that Tα-1 accelerates the replenishment and maturation of thymocytes, stimulates differentiation into active T cells and restores T-cell function by T-cell-mediated antibody production [7]. It was also shown that Tα-1 increases intrahepatic NKT cells and CTLs in CHB patients [6]. Thus Tα-1 therapy is used for the treatment of CHB either as monotherapy or combined with other drugs.

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2. Monotherapy of Tα-1 in chronic hepatitis B

Tα-1 treatment in CHB was started from 1990s [8]. Five randomized, controlled trials have been conducted to investigate efficacy and safety of Tα-1 compared with no antiviral treatment in patients with CHB [8-12]. Meta-analysis [13] of these studies (353 patients) has shown that compared with no antiviral treatment, Tα-1 at a dose of 1.6 mg (twice weekly subcutaneous injection) for 26 weeks is effective in suppressing viral replication in both HBeAg-positive and HBeAg-negative CHB patients, especially a delayed virological response until 12 months after the cessation of treatment with odds ratio of 2.67. Whereas there was no difference in the biochemical response between thymosin and untreated group, another study showed that genotype B, compared to genotype C, is associated with a higher response rate to Tα-1 of therapy. Genotype, presence of precore mutation and Tα-1 therapy were independent predictors to complete response [14].

Though 'effective' has been demonstrated in these early studies, it is only modest and far from satisfactory because more sensitive HBV DNA assays based on polymerase chain reaction amplification with lower limits of detection of 15 – 20 IU/ml instead of dot blot have been widely used in clinical practice. It is well known that long-term effective suppression of HBV replication will prevent progression of CHB to liver cirrhosis, decompensated cirrhosis, end-stage liver disease and hepatocellular carcinoma.

Compared with IFN-α, which is also an effective antiviral immunomodulatory drug in CHB, monotherapy with Tα-1 may have more beneficial effects. Four randomized studies [15-18] observed the efficacy of Tα-1 versus IFN-α treatment of CHB. Meta-analysis [19] of these studies (199 patients) has shown that 6 months of Tα-1 therapy is as effective as IFN-α, whereas better virological response and biochemical response appeared at the end of follow-up (6 months post-treatment) with odds ratio of 3.71 and 3.12 respectively.

However, three of the four studies were conducted in HBeAg-negative patients with conventional IFN-α. Also the beneficial virological response and biochemical response were achieved 6 months post-treatment, which is believed to be the effects of stimulation of the immunological functions. Therefore, Tα-1 has been used in combination therapy of either lamivudine or IFN-α.

3. Combination therapy of Tα-1 in chronic hepatitis B

It seems that combination therapy with Tα-1 is promising. A meta-analysis [20] of eight controlled trials designed to study the combination of Tα-1 (for 24 – 52 weeks) and lamivudine (52 weeks) in 583 CHB patients, Tα-1 and lamivudine combination therapy showed superior effects than lamivudine monotherapy in terms of biochemical response (80.2% vs 68.8%, $p = 0.01$), virological response (84.7% vs 74.9%, $p = 0.002$), and HBeAg seroconversion (45.1% vs 15.2%, $p < 0.00001$). Besides lamivudine, another open-label study compared therapy of Tα-1 plus famciclovir versus famciclovir monotherapy in HBeAg-positive patients. At the end of follow-up of 52 weeks, 15.6% of patients in the combination group achieved a complete virological response compared to no patient in monotherapy [21].

Other studies showed that combination of IFN-α with Tα-1 may provide a safe and effective therapeutic approach in the treatment of CHB patients [22,23]. A Chinese meta-analysis [24] compared the efficacy of IFN and Tα-1 combination therapy with IFN monotherapy for HBeAg-positive CHB. Seven randomized controlled trials were included (535 patients). It showed that combination therapy was remarkably more effective than monotherapy of HBV-DNA suppression both at the end of the treatment (54.9% vs 36.3%, $p < 0.01$) and the follow-up (58.6% vs 30.7%, $p < 0.01$). ALT normalization, HBeAg loss and HBeAg seroconversion had the similar results. Most importantly the HBsAg loss rate of the combination therapy group was significantly higher than that of the monotherapy group at the end of the follow-up (9.8% vs 3.7%, $p < 0.05$). However, a later prospective, multicenter, randomized, open-label study did not show efficacy of adding short-term (first 12 weeks) Tα-1 to PEG-α-2a combination therapy in HBeAg-positive CHB [25].

As suggested by Asian-pacific guideline of HBV treatment [26], Tα-1was effective to treat CHB with fixed duration and minimal side effects. However, well-designed studies are needed. Recently, a large-scale, randomized, open-label, multicenter study was conducted. The aim was to investigate efficacy and safety of combination therapy of Tα-1 plus entecavir in HBV-compensated cirrhosis. The benefit of using Tα-1 and entecavir is to combine both of the immune control and potent viral suppression to treat HBV. Two hundred patients with histological confirmed early cirrhosis of F4 (NCT 01938820), and six hundred clinically diagnosed compensated liver cirrhosis (NCT 01943617) were randomly assigned in a 1:1 ratio. One arm was entecavir alone for 2 years; the other was entecavir for the first 0.5 year, then entecavir plus Tα-1 for 1 year, and then entecavir for another additional 0.5 year. Patients will be assessed at baseline, at every 6 months for blood count, liver function test, HBVDNA, AFP, prothrombin time, liver ultrasonography, and Fibroscan. These two studies were started at 2013 and final results could be expected in the year of 2016.

These are important investigations in immunomodulatory therapy for chronic HBV infection. Up to now, Tα-1 has been used in > 300,000 patients and 70 clinical studies, including HBV-induced cirrhosis and old patients. Unlike IFN-α, thymosin has a favorable safety profile, no serious adverse effects were observed in most studies and it does not appear to exacerbate the side effects of IFN therapy; it is an important basis for more combination therapy exploration of Tα-1 with other drugs in the future.

4. Conclusion

As an immunomodulatory agent, Tα-1 has a beneficial effect in chronic viral hepatitis. In CHB, Tα-1 monotherapy is effective in suppressing viral replication compared with untreated control or conventional IFN-α. Most of combination therapy of Tα-1 plus either lamivudine or IFN-α showed better effects on HBV DNA suppression and HBeAg seroconversion. Recently clinical studies of Tα-1 combined with entecavir on the treatment of HBV-cirrhosis are ongoing.

5. Expert opinion

Though nucles(t)ide analogs such as entecavir and tenofovir are effective and potent in suppressing virus replication, none of them can eliminate HBV. The studies presented that Tα-1 application, either alone or combination, is helpful in HBV virus suppression. However the efficacy is not strong enough to be the principle anti-HBV medicine in CHB treatment. The promising strength of Tα-1 might be stimulating a successful host immune response to eliminate HBV in the system, which is the important treatment goal of HBV therapy.

Therefore it is worthy of investigating the efficacy of combination therapy of Tα-1 with entecavir or tenofovir in CHB, which is rarely reported. As Tα-1 has a very good safety profile, the studies to evaluate the efficacy of combination therapy of Tα-1 and entecavir or tenofovir could be started in HBV-related compensated liver cirrhosis, which has the higher priorities of treatment to decrease disease progress. Both of the surrogate makers including HBV undetectable rate, HBeAg/HBsAg seroconversion, and the hard endpoints including complications of decompensated cirrhosis, HCC and survival rate should be evaluated in the long-term treatment. Also further studies to improve the treatment indications, dose and durations are needed.

Declaration of interest

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Notice of correction

Please note the sentence "This paper is part of a supplemental issue, sponsored by SciClone" was added to the declaration of interest section after initial online publication of this article (2nd February 2015).