Results of clinical trials of thymosin α_1 in chronic hepatitis B conducted in Taiwan, Singapore, Japan and Italy

D. L. Horwitz
SciClone Pharamceuticals, San Mateo, California, U.S.A.

Introduction

The prevalence of chronic hepatitis B (CHB) in Asian countries is among the highest in the World. While in the Western Countries hepatitis B exposure most often occurs in adult life, often through sexual transmission or intravenous drug abuse, neonatal or childhood exposure appears to be more common in Asia. In spite of widespread hepatitis B immunization in these countries, chronic hepatitis B continues to be a major public health problem. Both the high prevalence of chronic hepatitis B in Asia and the distinctive epidemiological patterns have led many clinical investigators to conduct clinical trials in Asia. SciClone Pharmaceuticals is conducting trials of thymosin α_1 ($T\alpha_1$) therapy in Singapore and Taiwan, and in conjunction with Schering-Plough KK trials are also being conducted in Japan. To date, the trials in these three countries have enrolled over 300 patients, with more than two thirds receiving $T\alpha_1$ treatment and the remaining subjects being in untreated control groups.

Taiwan

SciClone Pharmaceuticals is the sponsor of an ongoing open label "Multicenter Study of Thymosin Alpha 1 in the Treatment of Chronic Hepatitis B" in Taiwan. 158 patients who met the following admission criteria have been recruited for this trial:

1. age 18 to 75,
2. HBsAg positive for at least six months,
3. elevated serum alanine aminotransferase (ALT) on at least two occasions at least two months apart, with each value ≥ 2 and ≤ 10 times the upper limit of normal,
4. HBeAg and HBV DNA positive on at least two determinations at least one month apart within a period of four months before entry into the study,
5. a liver biopsy within 12 months prior to entry into the study,

Table I. Interim results from $T\alpha_1$ Taiwan CHB trial.

	Control	$T\alpha_1$ 6 months	$T\alpha_1$ 12 months
Number completed 18 months treatment and follow-up	24	26	24
ALT normalized	11–46%	15–58%	12–50%
HBeAg clearance[a]	2–8%	11–42%	10–42%
HBV DNA clearance	9–38%	14–54%	11–46%
HBeAg and HBV DNA clearance[a]	2–8%	10–38%	8–33%

[a] $p < 0.05$ $T\alpha_1$ vs. control

6. the final HBV DNA during the screening period was not less than 50% of the previous value,
7. no previous interferon therapy or other type of immunotherapy within 12 months prior to entry into the study,
8. no adrenocorticoid steroid therapy within six months prior to entry into the study.

Patients meeting the admission criteria were randomly assigned to receive one of the following treatments: group I, Tα1 1.6 mg twice weekly for six months followed by 12 months observation, group II, Tα1 1.6 mg twice weekly for 12 months followed by six months observation, and group III untreated.
A complete virologic response to treatment is defined as serum HBV DNA and HBeAg negative at the end of the study. A clinical response to treatment is defined as normalization or near normalization (≤ 1.3 X upper limit of normal and ≥ 50% decrease) of ALT at the end of the study. A histologic response is defined as improvement in the histological grading of a liver biopsy according to the grading method of *Knodell.*
An interim analysis was performed on the data from 74 patients completing 18 months of treatment and observation out of the 98 patients enrolled at one of the three centers participating in this study. The results are shown in table I. Response rates are approximately equal (defined as HBV DNA and HBeAg negative) in the 6-month (38.5%) and 12-month treatment groups (33.3%), with both being significantly ($p < 0.05$) greater than the response rate in the untreated controls (8.3 %) (1).

Singapore

SciClone Pharmaceuticals is the sponsor of two ongoing open label trials in Singapore: "Thymosin Alpha 1 in the Treatment of Chronic Hepatitis B" and "Thymosin Alpha 1 on the Treatment of Asymptomatic Hepatitis B Carriers." Approximately 100 patients who meet the following admission criteria will be recruited for each of these trials:

1. age 18 to 64,
2. HBsAg positive for at least six months,
3. for the chronic hepatitis B study, elevated serum alanine aminotransferase (ALT) on at least two occasions at least four weeks apart, with each value ≥ 2 times the upper limit of normal or the mean of 3 ALTs obtained during screening > 2 times the upper limit of normal, or, for the hepatitis B carriers study, elevated serum alanine aminotransferase (ALT) on at least two occasions at least four weeks apart, with each value < 2 times the upper limit of normal or the mean of 3 ALTs obtained during screening < 2 times the upper limit of normal,
4. HBeAg and HBV DNA positive on at least two determinations at least four weeks, a liver biopsy within 12 months prior to entry into the study,
5. the final HBV DNA during the screening period was not less than 50% of the previous value,
6. no previous interferon therapy or other type of immunotherapy within 12 months prior to entry into the study,
7. no adrenocorticoid steroid therapy within six months prior to entry into the study.

Patients meeting the admission criteria were randomly assigned to receive one of the following treatments: group I, Tα1 1.6 mg twice weekly for six months followed by six months observation, group II, Tα1 1.6 mg twice weekly for 12 months followed by six months observation, and group III, untreated and observed for 12 months.
A complete virologic response to treatment is defined as serum HBV DNA and HBeAg negative at the end of the study. A histologic response is defined as improvement in the histological grading of a liver biopsy by at least 25% according to the grading method of *Knodell.*
Because the two trials in Singapore are ongoing, no conclusions can be drawn at this time.

Japan

Schering-Plough KK is developing thymosin α_1 for chronic hepatitis B in Japan in partnership with SciClone Pharmaceuticals. In a "Phase I Single Rising Dose and Multiple Dose Study of Thymosin α_1 in Japan" eight healthy male volunteers were treated with two single doses of thymosin α_1, 0.8 mg

and 3.2 mg or 1.6 mg and 6.4 mg SQ, and eight healthy male volunteers were treated with seven daily doses of thymosin α_1 3.2 mg SQ. Clinical pharmacology, safety and pharmacokinetic parameters were measured. The Phase I study enabled Schering-Plough KK to commence a "Phase II Clinical Study" which includes 60 patients with a diagnosis of chronic hepatitis B. The patients are stratified based on HBV DNA level and genotype and then randomly assigned to one of the following treatments: group I, $T\alpha_1$ 1.6 mg twice weekly for 24 weeks, group II, $T\alpha_1$ 0.8 mg daily for six days each week for two weeks and then twice weekly for 22 weeks, group III, $T\alpha_1$ 1.6 mg daily for six days each week for two weeks and then twice weekly for 22 weeks, or, group IV, $T\alpha_1$ 3.2 mg daily for six days each week for two weeks and then twice weekly for 22 weeks. Efficacy parameters include liver biopsy, ALT and HBV DNA. Because the Phase II trial in Japan is ongoing, no conclusions can be drawn at this time

Italy

The Italian National Research Council sponsored an open label trial of "Combination Low-Dose Lymphoblastoid Interferon and Thymosin α_1 Therapy in the Treatment of Chronic Hepatitis B." A total of 15 patients with chronic hepatitis B, including eleven who failed to respond to standard interferon-α_{2b} therapy and four, who were interferon-naive, who met the following admission criteria were recruited for this trial:

1. age 18 to 65,
2. HBsAg positive for at least 12 months,
3 HBV DNA positive on at least three determinations at least one month apart within a period of six months before entry into the study,
4. elevated ALT for at least six months prior to study entry, with each value $\geq$ 1.5 times the upper limit of normal,
5. a liver biopsy within six months prior to entry into the study,
6. no previous interferon or other antiviral therapy or immunosuppressive therapy within 12 months prior to entry into the study.

Patients meeting the admission criteria were treated with $T\alpha_1$ 1 mg subcutaneously (SQ) each morning for four days followed by the first lymphoblastoid interferon (L-IFN) 3 million units intramuscularly (IM) on the evening of day 4. Beginning with the second week and for the subsequent 25 weeks patients self injected $T\alpha_1$ 1 mg SQ each Monday and Thursday morning and L-IFN 3 million units IM 12 hours later each Monday and Thursday.
Patients were followed for 12 months after the last treatment. A positive response to treatment was defined as negative serum HBV DNA and normal serum ALT at 18 months from entry into the trial. Liver biopsies were performed within six months prior to entering the trial and six months after the last injection of study medication.

Table II. Results from $T\alpha_1$ Italian CHB trial.

Number of patients HBV DNA negative and ALT	Total treated	Previous IFNα2b failures
Normal	15	11
6 Months	6–40%	4–36%
12 Months	8–53%	5–45%
18 Months	9–60%	6–55%

This trial has been completed and the results are shown in table II. Nine (60%) of the 15 patients, including 6 (55%) of the eleven patients who previously failed to respond to standard interferon-α_{2b} therapy, responded to combination $T\alpha_1$-L-IFN therapy by losing HBV DNA and normalizing serum ALT. Seven of the nine responders became HBeAg negative. Six (67%) of the nine responders became HBsAg negative and anti-HBsAg positive (2, 3).

Discussion and summary

SciClone Pharmaceuticals is conducting trials of thymosin α_1 ($T\alpha_1$) therapy in Singapore and Taiwan, and in conjunction with Schering-Plough KK trials are also being conducted in Japan. To date, the trials in these three countries have enrolled over 300 patients, with more than two thirds receiving $T\alpha_1$ treatment and the remaining subjects being in untreated control groups.

In Taiwan, the trial is comparing the standard 6-month course of $T\alpha_1$ (1.6 mg subcutaneously twice weekly) with a 12-month course. Interim analysis of data on 74 subjects from one center has shown approximately equal response rates (defined as HBV DNA and HBeAg negative) in the 6-month (38.5%) and 12-month treatment groups (33.3%), with both being significantly ($p < 0.05$) greater than the response rate in the untreated controls (8.3%).

One of the two Singapore trials is examining whether $T\alpha_1$ will also be effective in CHB patients who do not have elevated ALT levels.

In Japan, a dose-ranging trial will study whether higher or lower doses of $T\alpha_1$ may improve efficacy, and whether an induction period of daily dosing will be helpful.

The Italian National Research Council has sponsored a pilot trial of combination therapy with $T\alpha_1$ and interferon alpha in CHB. The data indicate a conversion rate to HBsAg negative status in 40% of subjects.

Adverse drug experiences have been negligible.

References

1 Chien RN, Liaw YF. Thymosin alpha 1 in the treatment of chronic hepatitis B: An interim report. Taiwan GI Specialist Association Spring Meeting. Taiwan. March 1996 (abstract)

2 Rasi G, DiVirgilio D, Colella F, Sinibaldi-Vellebona P, Pierimarchi P, Innocenti F, Favalli C, Garaci E (1993) Combined treatment with thymosin α_1 and interferon-α in B and C virus chronic hepatitis. Third International Symposium on Combination Therapies. Houston; October 29–31 (abstract)

3 Rasi G, Mutchnick MG, DiVirgilio D, Pierimarchi P, Sinibaldi-Vellebona P, Colella, Favalli C, Garaci E (1994) Combination low-dose lymphoblastoid interferon (L-IFNα) and thymosin α_1 (Tα_1) therapy in the treatment of chronic hepatitis B. Hepatol 20(4, pt 2): 811