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REPORT

A Life-Saving Drug Discovered In the United States Over 20 Years Ago Is Saving Lives Around the World... But Not Yet Here

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In 1981, The Life Extension Foundation featured a headline article about the benefits of an immune boosting agent that showed promise in treating cancer and viral hepatitis. The reason this article was published was the anticipation that the FDA would soon approve thymosin alpha-1, a synthetic version of a natural thymic peptide, as a drug to save American lives.

Unfortunately the drug stumbled along the way. In the key phase III randomized double blind trial, it failed to reach statistical significance in a 90 patient study by 1 patient. It did much better in Europe and Asia and was long-ago approved in Italy and 20 other countries in Asia and the Americas including China, India, the Philippines, Argentina, Peru and Mexico. Thymosin alpha-1 is also used effectively in combination as adjuvant therapy in treating certain cancers and hepatitis viruses.

Thymosin alpha-1 should be available to Americans right now, but has not yet met muster with the more rigorous standards required by the FDA. Hopefully that will change in the next two to three years, as a large pivotal multicenter phase III trial involving over 1000 patients with hepatitis C has been initiated with thymosin alpha-1 in the U.S. in combination with pegylated interferon alpha-2a.

In this article, we relate the results of completed clinical studies indicating that thymosin alpha-1 could potentially save many Americans lives if it were available now.

Immune system regulation and response is critical in the treatment of a variety of diseases, including hepatitis B and C, influenza, AIDS, cancer and other immunodeficiency diseases. In some cases, however, the current treatment for these widespread diseases—chemotherapy, for instance—weakens the immune system, putting patients at risk of predatory infections.

A peptide called thymosin alpha-1 has been extensively studied for its beneficial effects on immune response and its therapeutic value. In more than 70 studies, thymosin alpha-1 has exhibited immunomodulatory activity and demonstrated benefits, whether used alone or in conjunction with a conventional therapy. Many effects of thymosin alpha-1 appear to be synergistic with those of other cytokines (alpha interferon and interleukin-2), and thymosin alpha-1 may work best in combination with other immunomodulators.

Originally isolated from the thymus gland, thymosin alpha-1 is an amino-terminal acylated peptide of 28 amino acids. It is found in highest concentrations in the thymus but has also been detected in spleen, lung, kidney, brain, blood and a number of other tissues.

Enhancing immune function

Thymosin alpha-1's immunomodulatory activities are centered primarily on the augmentation of T-cell function, and it shows promise in the treatment of a wide variety of diseases. Thymosin alpha-1 has been shown to increase production of interferon, interleukin 2 (IL-2), and interleukin 3 (IL-3).(1-7) Thymosin alpha-1 has been shown to increase natural killer cell activity(8-10) and enhance production of CD3 and CD4 and CD8 cells in patients with chronic hepatitis B(11) and cancer.(12) Treatment with thymosin alpha-1 has also been shown to decrease replication of the HIV-I virus in human peripheral blood cells, and it has been reported to inhibit the in vitro growth of various non-small-cell-lung-cancer cell lines.(13,14)

Hepatitis B

Chronic hepatitis B is a widespread disease associated with significant morbidity and mortality. At least 300 million people worldwide are chronically infected with the hepatitis B virus, with carrier rates as high as 20% in some populations. Chronic



hepatitis B is associated with increased risk for developing cirrhosis, liver failure and hepatocellular carcinoma.

Interferon was the first therapy approved for treatment of hepatitis B in the United States and Europe. Initial enthusiasm for this therapy has waned, however, with the realization that response rates are low and relapses are common. Interferon therapy is also associated with significant side effects. The most common adverse events associated with interferon therapy are flu-like symptoms, fatigue, anorexia, and central nervous system and psychiatric reactions. The incidence of depression and suicidal behavior has only recently been fully appreciated, with a significant increase in depression during the sixth month of interferon therapy.(15)

Lamivudine has recently been approved in the United States and Europe as a treatment for hepatitis B, and famciclovir is still under investigation. These anti-viral drugs effectively reduce hepatitis B viral counts and liver enzyme elevation while the therapy continues. Unfortunately, there is no evidence that these antiviral agents produce sustained responses in a significant number of patients. When therapy is discontinued, viral counts and elevated liver enzymes usually return to pretreatment levels.

Interest in using thymosin alpha-1 for treatment of human hepatitis B is based on the fact that it is an immunomodulator that can trigger maturational events in lymphocytes, augment T cell function and promote reconstitution of immune defects.

In clinical studies on hepatitis B patients, thymosin alpha-1 has been primarily investigated as monotherapy, but promising results have also been obtained when thymosin alpha-1 is used in combination with interferon. In addition, thymosin alpha-1 has an excellent safety record. In treatment of over 3,000 patients with a range of diseases including hepatitis B and hepatitis C, thymosin alpha-1 has been well tolerated and is not associated with any significant side effects.

Four randomized controlled studies have investigated the safety and efficacy of thymosin alpha-1 monotherapy for the treatment of chronic hepatitis B. These studies show that thymosin alpha-1 promotes disease remission in 25% to 75% of the patients treated. Two of the studies resulted in statistically significant findings, and the third trial was statistically significant for the primary treatment center. When all the studies are considered together in a meta-analysis, the results show that six months treatment with thymosin alpha-1 almost doubles the sustained response rate (36%) compared to controls (19%).

Data from the four studies were also compiled and analyzed using intent-to-treat analysis. Intent-to-treat analysis includes all patients randomized to a particular treatment group, whether or not they completed treatment or follow-up. Statistically this is the most conservative approach, and is most commonly required by the FDA and other nations' health authorities.

The overall percentage of responders in the thymosin alpha-1-treated group increased from 10% at 6 months to 25% at 12 months and 36% at last assessment. This compares to remission in the control groups of 6% at 6 months, 11% at 12 months and 19% at last assessment. Obviously, the long-term sustained response was significantly in favor of thymosin alpha-1 compared to control.

While these studies suggest that thymosin alpha-1 is an effective monotherapy for hepatitis B, a number of other studies suggest that it can work in synergy with existing immune modulators or antiviral agents. Because of its excellent safety profile, thymosin alpha-1 may be combined with other therapies such as interferon or anti-viral drugs like famciclovir to enhance their efficacy without increasing toxicity.

This was examined in a study testing a combination of low-dose lymphoblastoid interferon (L-IFNa) and thymosin alpha-1 in the treatment of 15 patients with hepatitis B. The thymosin alpha-1 plus L-IFNa combination treatment resulted in an overall response of 60%, with disease remission achieved in 55%. No reactivation of disease was seen in any of the sustained responders when followed beyond the 12-month follow-up period. The dose of L-IFNa was a fraction of the

Another Potentially Effective Adjuvant Therapy

Polaprezinc is an approved drug in the treatment of ulcers in Japan. It is a relatively new drug, with the first publications surfacing in 1991.

Polaprezinc appears to remain in the stomach juice without rapid dissociation and adhere to ulcerous lesions (preferentially), after which zinc and L-carnosine are released to initiate a cascade of events that help heal the ulcer. It has high efficacy, without serious side effects (Matsukura, Tanaka, *Biochemistry (Mosc)* 2000, Jul 65(7):817-23).

It may have an inhibitor role on *H. pylori*, the bacteria that causes many stomach ulcers. One study (Kashimura et al, *Aliment Pharmacol Ther* 1999, April; 13(4): 483-7) showed that antibiotics plus polaprezinc resulted in a near complete eradication of *H. pylori*, while antibiotics alone saw almost 20% failure to resolve the infection.

How this drug could save lives

Polaprezinc may have life-saving properties that go beyond ulcer treatment.

Proprezinc suppresses a growth factor called nuclear factor kappa beta. Certain cancer cells express this growth factor to escape the cytostatic control of interferon-Accutane therapy and the cytotoxic effects of certain chemotherapy drugs. While there is a molecular rationale to combine polaprezinc with some cancer therapies, no human studies have been done to support this. Since polaprezinc is non-toxic, there appears to be no downside for those with certain types of cancer to use it. Cancer patients do not have a choice, however, since polaprezinc is not approved for sale in the United States.

There is a human study where polaprezinc was combined with alpha interferon in the treatment of hepatitis C. This study was done on a group of Japanese infected with the Type 1b hepatitis C. About 70% of American hepatitis C patients are infected with this strain that is resistant to interferon-ribavirin therapy. Here are the results of this study

total standard dose usually given.

In Hong Kong, another study evaluated the response in 32 patients with hepatitis B after six months' treatment with thymosin alpha-1 plus famciclovir.(16) After the treatment period and 12 months of follow-up, three patients demonstrated disappearance of serum indicators of hepatitis B infection (HBV DNA and HBeAg). Furthermore, 27.3% of combination thymosin alpha-1 plus famciclovir-treated patients had a significant improvement in liver histology.

The combination thymosin alpha-1 plus famciclovir was well tolerated, and no side effects were reported. These results are highly promising since immune tolerant patients, like the ones in the study, usually do not respond to any available drug therapy.

Hepatitis C

Hepatitis C is recognized as a global health problem, with an estimated worldwide prevalence of more than 200 million victims and no foreseeable vaccine. As in hepatitis B, thymosin alpha-1 has been shown to be safe and effective for the treatment of chronic hepatitis C when used in combination with alpha interferon (IFNa). Although the hepatitis B and C viruses are not structurally related, they are similar in that they are both associated with a high incidence of liver disease, including cirrhosis and hepatocellular carcinoma.

Current management of hepatitis C is centered on the use of interferons. Unfortunately response occurs in a minority of patients and sustained response in fewer. Recently, the FDA approved a new combination therapy, Rebetron™ (ribavirin and interferon alfa-2b) to treat chronic hepatitis C patients who have relapsed following standard interferon treatment. The new combination shows fewer relapses than interferon alone, but many hepatitis C patients do not obtain a complete response. The dissatisfaction with the treatment response rate and the sustained response rate has led to studies of interferon combined with other modalities, such as thymosin alpha-1.

Three studies have investigated the therapeutic effect of thymosin alpha-1 in combination with interferon for treatment of chronic hepatitis C.(17-19) The data show that thymosin alpha-1 in combination with interferon is safe and effective and significantly superior to interferon alone. With thymosin alpha-1 plus interferon combination therapy, the end-of-treatment and sustained responses are twice that obtained with interferon alone.

Pooled intent-to-treat analysis of 121 patients from the three studies revealed an end-of-treatment biochemical response (ALT liver enzyme reduction) of 45% in the thymosin alpha-1-plus-interferon combination treatment group compared to 22% in the interferon monotherapy group. Sustained response was observed in 9% of patients treated with interferon alone, compared to 22% in the thymosin alpha-1 plus interferon combination therapy.

Meta-analysis indicates that the combination of thymosin alpha-1 and interferon was more than three times better at normalizing liver enzyme elevation at the end of treatment than interferon alone. In addition, meta-analysis indicated that thymosin alpha-1 plus interferon combination therapy was also superior to interferon monotherapy for sustained biochemical response.

The United States National Institutes of Health (NIH) Consensus Meeting held in March 1997 reviewed new data in the treatment of hepatitis C. The NIH CHC conference concluded that thymosin alpha-1, when used in combination with IFN-a, is "the most promising of the cytokines or immunomodulators tested thus far."(20)

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showing the percentage of complete response (viral eradication) in hepatitis C patients given the following three regimens:

Interferon (monotherapy)	Interferon plus zinc	Interferon plus polaprezinc
20%	11%	53.3%

This study was published in the journal Biological Trace Elements Research (Vol 75, 2000). We identified several flaws in the design of this study and would have preferred if had been done with better controls. But here again, if polaprezinc were allowed to be sold in the United States, at least hepatitis C patients could make their own choice! Safety is not an issue with this ultra-safe drug.

Only 20% of hepatitis C patients who take interferon by itself achieve complete response, whereas the possibility of improving the complete response rate may be significantly improved when polaprezinc is taken with the interferon.

The suggested dose for cancer patients and hepatitis C patients is 150 mg of polaprezinc, twice a day. If you don't live in Japan, it is very difficult to obtain this unique compound of carnosine and zinc.

Optimal treatment of hepatitis C might involve both Thymosin alpha-1 and polaprezinc in conjunction with alpha-interferon (and possibly ribavirin). This scientific approach to eradicating hepatitis C infection is not available to Americans.

REPORT

HIV

Stimulation of the immune system, especially in combination with antiviral agents, has received considerable interest as a potential means to treat acquired immune deficiency syndrome (AIDS) and HIV-infected patients. Studies have shown a high degree of immune restoration from the combined administration of thymosin alpha-1 and alpha interferon (IFN α). Thymosin alpha-1 in combination with AZT and IFN α has been investigated for treatment of HIV-infected patients.

At the University of Rome, a group of researchers conducted a study to investigate the combination of thymosin alpha-1, IFN α and AZT for treatment of HIV-infected patients with CD4 counts of 500 or lower.(21) The study included seven patients in each of four treatment groups: thymosin alpha-1 plus IFN α plus AZT; thymosin alpha-1 plus AZT; IFN α plus AZT; and AZT.

Treatment was continued for 12 months for the majority of patients, with up to 18 months for a smaller cohort of patients. After one year, the thymosin alpha-1 plus IFN α plus AZT combination therapy resulted in a statistically significant increase in CD4 cells and stimulation of lymphocyte cytotoxic activity against natural killer-sensitive target cells compared with the other three treatment groups.

Vaccines

Immune senescence, considered an aging process, has been related to a gradual decline in thymus function and thymic hormone production. The lack of thymic hormones may contribute to the decline in immune function, particularly the T cell component.(22-24) In the elderly, antibody response after vaccination is compromised when compared to response in young.(25,26) This may be one factor that accounts for insufficient efficacy of certain vaccination programs (e.g., influenza).

A similar diminished antibody response has been reported in patients with end-stage renal disease (ESRD) and in hemodialysis patients. In hemodialysis patients, this has been attributed to incompetence in T cell-mediated immune responses.(27-31) Since thymosin alpha-1 can enhance T-cell-dependent specific antibody production, the addition of thymosin alpha-1 to vaccination programs for immunocompromised individuals should be effective.

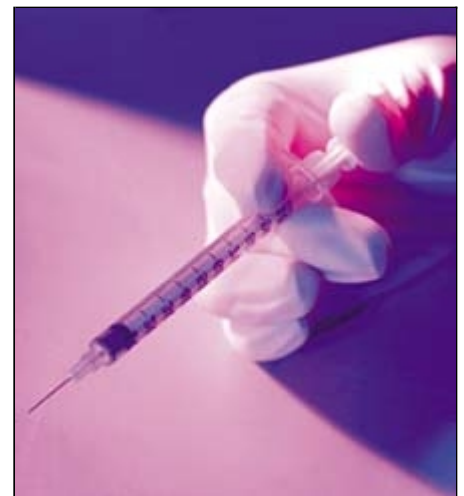
Six clinical studies have been completed that evaluated the efficacy of thymosin alpha-1 as an adjuvant for influenza and hepatitis B antiviral vaccines in subjects immunocompromised due to age or hemodialysis. When compared to vaccine plus placebo, administration of thymosin alpha-1 in conjunction with vaccine increased and sustained the specific antibody response, increased protection against illness, and overcame previous lack of specific antibody response and age-associated decline in specific antibody response. No serious adverse effects were observed in any of the studies.

Cancer

The therapeutic usefulness of thymosin alpha-1 has been examined in several types of cancers. The rationale for such use is that thymosin alpha-1 has efficacy in several animal cancer models and has been shown to improve immune function. Patients with some cancers have depressed cellular immunity, and progression of some cancers appears to be related to impaired suppression of the tumors by the immune system. This has been shown to be the case for hepatocellular carcinoma, non-small-cell lung cancer and melanoma.



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Primary liver cancer is the most prevalent malignant disease in the world, killing up to 1.25 million people every year. Hepatocellular carcinoma accounts for more than 80% of all primary liver tumors and has a worldwide annual incidence of approximately one million new cases.(32) Although hepatocellular carcinoma is a common malignancy in Africa and Asia, it accounts for approximately 4,000 to 6,000 cases per year in the United States.(33)

When identified in its early stages, hepatocellular carcinoma can be treated with surgical resection or liver transplantation, and some patients may be cured. However, sometimes the disease is not amenable to surgical treatment, either because of tumor size or because of poor liver function. In these situations the prognosis is dire. Other treatment approaches have been tried when surgery or liver transplantation are not feasible. Chemotherapy results are mixed.

One study involving 12 patients examined thymosin alpha-1 for treatment of primary liver cancer.(34) The patients were treated with thymosin alpha-1 for six months, in addition to transcatheter arterial chemoembolization (TACE) mixed with 40 mg to 60 mg of doxorubicin. Patients treated with the combination of thymosin alpha-1 plus TACE showed longer survival compared to the control group treated with TACE alone.

Thymosin alpha-1 has also been used to treat non-small-cell lung cancer. This cancer accounts for approximately 75% of lung cancer cases, and current therapies such as radiation therapy and chemotherapy give disappointing results.(35,36)

A trial at George Washington University Trial involved 42 patients with localized, unresectable non-small cell lung cancer who were treated following radiation therapy for up to one year or until relapse.(37) Patients received either thymosin alpha-1 biweekly or placebo. Thymosin alpha-1 administration resulted in an improvement of T cell levels that had been depleted by radiation therapy and an increase in the percentage of lymphocytes expressing the pre-T cell and helper/inducer T cell surface markers. Both thymosin alpha-1 groups had statistically significant improvements in relapse-free and overall survival.

In a trial conducted in Italy involving 60 subjects, patients with non-small-cell lung cancer were treated with thymosin alpha-1 in combination with chemotherapy (cisplatin and etoposide) and interferon. Of the 55 evaluable patients, there was an overall response rate of 44%. Median survival was 12.6 months.(38)

Another form of cancer, malignant melanoma, is resistant to most forms of therapy. Response rates to dacarbazine (DTIC), the most active single agent, are approximately 17% to 20%, and have no impact on patient survival.(39-41) The effects of thymosin alpha-1 in combination with chemotherapy and cytokine therapy for treatment of malignant melanoma were examined in three trials in Italy with comparisons to historical controls.

In one trial,(42) in 26 treated patients evaluated by World Health Organization (WHO) criteria, there was an overall response rate of 50%. In another trial with the same combination treatment, 20 patients with stage III or IV metastatic melanoma were treated.(43) Ten patients responded to therapy for an overall response rate of 50%. Median survival time was 11.5 months with a median time to progression of 5.5 months. Importantly, 7 patients survived for more than 12 months and 3 patients were disease free after more than 3 years. In the third trial, there were 42 evaluable patients that showed an objective response rate of 36%, with a median time to progression of 5.5 months and median survival of 11 months.

Side Effects

In general, thymosin alpha-1 has an excellent history and shows a remarkable lack of side effects. Since 1979, it has been evaluated in more than 3,000 patients in over 70 clinical

Thymosin alpha-1 dosing regimen

The dosing regimen for thymosin alpha-1 varies with the disease it is treating.

In one study of hepatitis B, 1.6 mg of thymosin alpha-1 was administered twice weekly for six months.(1) Because its effectiveness can be increased by using it combination with other drugs, this dosage can be augmented with twice-weekly three MIU injections of low-dose lymphoblastoid interferon.(2)

In clinical studies, the dosage levels for hepatitis C were similar.(3)

In cancer studies, thymosin alpha-1 was often combined with several other drugs in a complex treatment regimen that might have included chemotherapy, interleukin-2 or interferon. Thymosin alpha-1 has shown efficacy against certain kinds of cancers, including hepatocellular carcinoma (HCC), non-small cell-lung-cancer and malignant melanoma.

In one study for hepatocellular carcinoma, patients were treated with .9 micrograms per square meter for six months, in conjunction with transcatheter arterial chemoembolization mixed with 40 mg to 60 mg of doxorubicin.(4)

In a monotherapy study for non-small-cell-lung-cancer, patients received .9 micrograms per square meter biweekly thymosin alpha-1 for one year after radiation treatment.(5)

In another study on lung cancer, thymosin alpha-1 was administered at a dosage of 1 mg/day on days 8 to 11 and 15 to 18 after chemotherapy. The thymosin alpha-1 cycles were alternated with interferon alpha-2a.(6)

As part of a multimodal treatment approach for malignant melanoma, thymosin was given after chemotherapy in a dose of 2 mg on days 4 to 7. On day 8, interleukin-2 was given until day 12. This cycle (chemotherapy/thymosin alpha-1/interleukin) was repeated every three weeks.(7)

In a study for HIV, patients were given a combination of AZT (500 mg/day), interferon (2 MIU BIW) and thymosin alpha-1 (1.0 mg BIW).(8)

studies. Administration has been in daily doses ranging from 0.6 mg/m² to 9.6 mg/m² and 1 mg to 16 mg for treatment periods ranging from 1 day to 18 months. No serious adverse experiences have been observed. Thymosin alpha-1 has been shown to be well tolerated even in patients with decompensated liver disease, renal disease requiring hemodialysis and primary immunodeficient individuals.



Thymosin alpha-1 has been shown to be well tolerated even in patients with decompensated liver disease. Because of its excellent safety profile, it may be combined with other therapies to enhance their efficacy without increasing toxicity

The lack of significant side effects with thymosin alpha-1 is in sharp contrast to other major immune modulators such as interferon and interleukin. The side effects and toxicities of these drugs make them difficult for most patients to tolerate. Interferon creates flu-like side effects (fever, chills, malaise and headaches), and interleukin causes significant edema in the lungs and elsewhere. Thymosin alpha-1, whether used alone or in conjunction with these drugs, has shown an impressive range of benefits.

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