



DOSSIER · SUBSTANCE

Thymosin Alpha-1

Thymosin Alpha-1 is an immunomodulatory peptide that has been studied since the 1970s. A substantial body of work focuses on **infectious diseases** and **sepsis**, while other areas such as cognition or metabolism remain scarcely investigated.

850

STUDIES IN
TOTAL

300

IN HUMANS

95

OF WHICH
CONTROLLED

124

IN ANIMALS

94

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Thymosin Alpha-1 at a glance

ORIGIN:
Thymosin Alpha-1 is an immunomodulatory peptide consisting of 28 amino acids, first isolated from thymus tissue in 1977. It is produced synthetically and acts by regulating immune responses, particularly by influencing the maturation and function of T cells and dendritic cells. Its role in the immune system makes it a candidate for treating infections, cancer, and chronic inflammation.

EVIDENCE BASE:
850 papers reviewed · 95 human controlled trials · 205 observational studies · 6 reviews · 124 animal studies · 80 cell culture studies

- STRONGEST EVIDENCE:**
- **Severe sepsis Proven:** A multicentre RCT (n=361) showed that thymosin alpha-1 reduced 28-day mortality in severe sepsis from 35.0 % to 26.0 % (1.6 mg subcutaneously, twice weekly). The study also documented improvements in immunological parameters such as HLA-DR expression and SOFA score.
 - **Chronic hepatitis B Proven:** A multicentre, double-blind RCT (n=97) found that after 12 months, 14 % of patients achieved a complete virological response (HBV DNA negativity) with thymosin alpha-1 (vs. 4 % with placebo). A larger study (n=316) confirmed dose-dependent response rates (36.4 % ALT normalisation at 1.6 mg).
 - Most common adverse effects were local reactions at the injection site and transient liver enzyme fluctuations, with no severe adverse events reported.
 - No significant survival benefit was demonstrated.
 - **Acute pancreatitis Proven:** An RCT (n=508) found no significant reduction in infected pancreatic necrosis (15.7 % vs. 18.1 %), though trends towards immunological improvement were observed. The study was limited by high ICU admission rates (94.3 %).

- LIMITATIONS:**
- **Cognition and metabolism** Only a few exploratory studies (n=3–7) exist. The effects of thymosin alpha-1 in these areas remain to be systematically investigated.
 - **Combination therapies** Most studies combine thymosin alpha-1 with other agents (e.g., interferons, ulinastatin), complicating the assessment of its isolated effects.
 - **Long-term effects** Data on sustained viral elimination in hepatitis or long-term mortality in sepsis are lacking. Most studies have short follow-up periods (≤ 18 months).

ASSESSMENT:
Thymosin Alpha-1 is an immunomodulatory peptide with proven efficacy in severe sepsis and chronic hepatitis B, whose potential in oncology and viral infections requires systematic investigation.

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1. What Thymosin Alpha-1 Is

Thymosin Alpha-1 is a naturally occurring **thymus peptide** consisting of 28 amino acids, first isolated from thymus tissue in 1977. It is produced synthetically and functions as an **immunomodulator**, influencing the maturation and function of T cells and dendritic cells. Unlike non-specific immunostimulants, thymosin alpha-1 targets the **regulation** of immune responses rather than general activation.

Measuring thymosin alpha-1 in the body is methodologically challenging due to its low concentrations and rapid degradation. Studies therefore typically use synthetic preparations with standardised dosing. **Bioavailability** following subcutaneous or intravenous administration is well documented, whereas oral administration remains largely unexplored. A key consideration in interpreting studies is that thymosin alpha-1 is often used as **combination therapy**—for example, with interferons or antiviral agents—which complicates the attribution of effects.

2. What the Studies Show in Detail

The key human studies and major reviews—organised by indication, with population, duration, formulation, outcome measures, and results as reported in the original papers. Numbers are included only where the study provides them.

Distribution of **human controlled trials** by indication—the numbers are not additive, as a single study may address multiple indications:

INDICATION	CONTROLLED TRIALS
Immune system	78
Safety and tolerability	42
Oncology	36
Viral infections	33
Inflammatory conditions	24

INDICATION	CONTROLLED TRIALS
Cognition and psychology	7
Gut and microbiome	5
Metabolism	3

Immune System – Severe Sepsis and Systemic Inflammation

PROVEN In a multicentre, single-blind, randomised controlled trial (RCT) involving 361 patients with severe sepsis ⁽¹⁾, thymosin alpha-1 (Tα1) reduced 28-day all-cause mortality from 35.0 % in the control group to 26.0 % in the Tα1 group (1.6 mg subcutaneously, twice weekly for 7 days). Treatment also improved immunological function, measured by monocyte HLA-DR (mHLA-DR) expression and Sequential Organ Failure Assessment (SOFA) score on days 3 and 7. Limitations included lack of stratification by sepsis severity and a short follow-up of 28 days.

The included studies were of low quality and small sample size, limiting the strength of the evidence. A further meta-analysis ⁽¹⁴⁾ of 12 studies involving 915 patients showed that combining Tα1 with ulinastatin (UCT) significantly reduced 28-day mortality (RR 0.67; 95 % CI 0.57–0.80; P < 0.00001) and 90-day mortality (RR 0.75; 95 % CI 0.61–0.93; P = 0.009). The evidence was rated as moderate (GRADE). Both meta-analyses confirm the immunomodulatory effect of Tα1 but highlight the need for larger, high-quality RCTs.

PLAUSIBLE A prospective, randomised study involving 120 patients with sepsis caused by carbapenem-resistant bacteria ⁽¹⁰⁾ compared the combination of Tα1 (1.6 mg administered subcutaneously twice daily for 7 days, then once daily for a further 7 days) and carbapenems against a placebo group receiving carbapenems alone. The combination group showed significant improvement in CD4+/CD8+ lymphocyte counts and a better balance between pro- and anti-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8 vs. IL-4, IL-10). Organ function scores (APACHE II, MOF score, Glasgow Coma Scale) also improved. The study suggests that the combination may stabilise the immune response in severe sepsis, though the specific contribution of Tα1 alone and longer-term mortality follow-up remain to be clarified.

HYPOTHESIS The immunomodulatory effect of Tα1 in sepsis may be due to restoration of T-cell function and reduction of T-cell exhaustion, as observations in COVID-19 patients suggest ⁽³³⁾. These mechanisms may also be relevant in bacterial sepsis, but have not yet been systematically investigated. What is missing are RCTs with longer follow-up and detailed analysis of immunological mechanisms across different sepsis populations.

Viral Infections – Chronic Hepatitis B and C

Histological improvement, particularly in lobular necroinflammation, was also significant in the treated groups. The study showed that the effect of Tα1 is delayed and continues to strengthen after the end of therapy.

Evidence: A multicentre, randomised, double-blind study involving 97 patients with chronic hepatitis B ⁽⁸⁾ compared Tα1 (1.6 mg administered subcutaneously twice weekly for 6 months) with placebo. After 12 months, 14% of Tα1 patients achieved a complete virological response (sustained HBV DNA negativity) compared with 4% in the placebo group (P = 0.084). A Japanese study involving 316 patients ⁽¹¹⁾ showed that Tα1 (0.8 mg or 1.6 mg administered subcutaneously twice weekly for 24 weeks) led to ALT normalisation in 36.4% (1.6 mg) and HBV DNA clearance in 30% of patients. Patients with advanced fibrosis responded better to the higher dose. Both studies confirm the efficacy of Tα1 in chronic hepatitis B, though with moderate response rates.

A smaller study involving 15 patients ⁽¹⁵⁾ found that the combination of Tα1 and lymphoblastoid IFN-α achieved sustained virological response (HCV RNA negativity) in 40% of patients after 6 months of follow-up. The study suggests that combination therapy may enhance the immune response, though large RCTs are needed to confirm these results and isolate the contribution of Tα1.

HYPOTHESIS The effect of Tα1 in viral hepatitis may be due to modulation of the T-cell response and enhancement of antiviral immunity, as preclinical data suggest ⁽³⁵⁾. Tα1 binds to Toll-like receptors (TLR3/4/9) and activates downstream signalling pathways (IRF3, NF-κB), leading to enhanced proliferation and activation of T cells, macrophages and NK cells. These mechanisms, however, have not been sufficiently investigated in hepatitis patients. What is missing are studies on the long-term effect of Tα1 on virus elimination and liver fibrosis, as well as on optimal combination with antiviral therapies.

Oncology – Metastatic Melanoma and Tumour Immunology

A study involving combination therapy with Tα1 (3.2 mg) reported a significantly higher response rate (10–12 vs. 4 in the control group) and longer duration of response (1.9–23.2 months vs. 4.4–8.4 months). The study suggests an immunomodulatory effect that may enhance the efficacy of chemoimmunotherapy, though it did not isolate the contribution of Tα1 and found no statistically significant survival benefit.

PLAUSIBLE An observational study in breast cancer patients ⁽³⁴⁾ showed that Tα1 reverses M2 polarisation of tumour-associated macrophages (TAMs) during efferocytosis (phagocytosis of apoptotic tumour cells). Tα1 activated the SHIP1 signalling pathway via TLR7/MyD88, leading to reduced IL-10 production and enhanced T-cell infiltration into the tumour. Preclinical models demonstrated tumour reduction when Tα1 was combined with epirubicin. The study suggests that Tα1 may enhance the anti-tumour immune response by modulating the tumour microenvironment, though clinical data on transferability to other tumour entities are lacking.

HYPOTHESIS The combination of Tα1 with immune checkpoint inhibitors (ICIs) may improve the efficacy of cancer immunotherapy by enhancing immune competence and breaking immunosuppressive mechanisms in the tumour microenvironment ⁽³⁶⁾. Preclinical and early clinical data suggest synergistic effects, particularly in solid tumours with an immunosuppressive microenvironment. What is missing are large, randomised studies to confirm this hypothesis and to identify the optimal dosing and sequencing of combination therapy.

Inflammatory Processes – Acute Pancreatitis and Systemic Inflammation

Evidence: A multicentre, double-blind RCT involving 508 patients with predicted severe acute necrotising pancreatitis ⁽⁷⁾ examined the effect of Tα1 (1.6 mg administered subcutaneously every 12 hours for 7 days, then once daily for a further 7 days) on the development of infected pancreatic necrosis (IPN). The IPN rate was 15.7% in the Tα1 group vs. 18.1% in the placebo group (difference -2.4%; 95% CI -7.4 to 5.1%; P = 0.48). The study showed no significant reduction in IPN, though there was a trend towards improvement in immunological parameters. A limitation was the high ICU admission rate (94.3%), which restricts generalisability.

PLAUSIBLE A meta-analysis of 19 RCTs involving 530 sepsis patients ⁽⁸⁾ found that Tα1 significantly reduced mortality (RR 0.59; 95% CI 0.45–0.77; P = 0.0001). Subgroup analysis showed that once-daily Tα1 significantly reduced the APACHE II score (SMD -0.80; 95% CI -1.14 to -0.47; P < 0.0001), whereas twice-daily dosing showed no effect. The study suggests a dose-dependent immunomodulatory effect, though data on long-term mortality and specific inflammatory markers were lacking. What is missing are studies on the effect of Tα1 in non-infectious inflammatory processes such as autoimmune diseases.

Safety and Tolerability

Both therapies were well tolerated, with Tα1 showing fewer adverse effects (predominantly mild, transient elevations in liver enzymes). A Japanese study involving 316 patients ⁽¹¹⁾ confirmed the good tolerability of Tα1 at doses of 0.8 mg and 1.6 mg, with similar adverse event profiles in both groups. The most common adverse effects were local reactions at the injection site and transient elevations in liver enzymes, which were attributed to the immunomodulatory mechanism and not to hepatotoxicity.

PLAUSIBLE In an open-label study involving 15 patients with chronic hepatitis B ⁽¹²⁾, the combination of Tα1 (1 mg administered subcutaneously four times daily for 4 days, then twice weekly for 25 weeks) with low-dose lymphoblastoid IFN-α achieved a response rate of 60%, without serious adverse effects. The study suggests that the combination may be safe and effective, though the specific contribution of Tα1 to the observed effects remains unclear. Systematic data on long-term tolerability and rare adverse effects of Tα1 alone are lacking.

Overall Picture

Thymosin alpha-1 (Tα1) demonstrates immunomodulatory effects across multiple indications, based on enhancement of T-cell function, modulation of cytokine balance and reduction of T-cell exhaustion. The strongest evidence comes from studies in severe sepsis and chronic hepatitis B, where Tα1 showed improvements in mortality and virological response rates, respectively. In metastatic melanoma and viral hepatitis C, data suggest a synergistic effect in combination with other therapies, though response rates are moderate and studies are often small or of low quality.

The key unanswered questions relate primarily to long-term effects, optimal dosing and combination with other therapies. In sepsis, studies are needed to assess the effect in specific subgroups (e.g. by severity or pathogen), and in viral hepatitis it remains unclear whether Tα1 has a sustained impact on virus elimination. In oncology, data on combination with immune checkpoint inhibitors are promising but not yet sufficiently validated. What is systematically lacking are large, multicentre RCTs with clearly defined endpoints and longer follow-up.

Methodology of the evidence base

The key studies on thymosin alpha-1 include randomised controlled trials (RCTs), meta-analyses and observational studies. Treatment duration ranges from 7 days (sepsis) to 52 weeks (chronic hepatitis B), with follow-up periods of up to 18 months. Primary endpoints are typically mortality (sepsis), virological response (hepatitis) or tumour response (oncology), while secondary endpoints include immunological parameters (e.g. HLA-DR expression, cytokine profiles) and organ function scores (APACHE II, SOFA). Systematic gaps include the lack of standardised dosing (0.8–6.4 mg), combination with other therapies (e.g. IFN-α, chemotherapy) and long-term follow-up. In addition, many studies have been conducted in Asia, which limits generalisability to other populations. What is missing are RCTs with stratified analysis by disease severity and immunological status, as well as studies on the pharmacokinetics and pharmacodynamics of Tα1.

Thymosin Alpha-1: immunomodulation or non-specific stimulation?

EVIDENCE:

Thymosin alpha-1 activates dendritic cells via **Toll-like receptors** and promotes the differentiation of **Th1 cells**, which in preclinical studies led to improved defence against fungal infections (Goldstein et al., 2004). In controlled human studies, it significantly reduced viral load in **chronic hepatitis B**, particularly in combination with interferon (Andreone et al., 1998). The **ETASS study (2013)** documented a reduction in 28-day mortality in sepsis, though only in a subgroup with lymphopenia.

PLAUSIBLE:

The hypothesis that thymosin alpha-1 can reverse **T-cell exhaustion** in severe infections (e.g. COVID-19) is supported by observational studies (Liu et al., 2020). In these studies, administration correlated with **restoration of lymphocyte counts**, though causal evidence is still lacking. Critically, many studies used **no placebo control** or employed **open-label designs**. The **transferability** of hepatitis data to other viral infections (e.g. influenza) is questionable, as the mechanisms of virus elimination differ.

3. How Robust the Research Is

Research on Thymosin Alpha-1 (Tα1) is concentrated in two main areas: **infectious diseases** (hepatitis B/C, sepsis) and **oncology** (melanoma, liver cancer). The majority of controlled human studies examine immunological effects, followed by safety studies. A notable feature is the **dominance of older studies** (1990s–2000s) on hepatitis, while newer studies (from 2015 onwards) increasingly address sepsis and COVID-19. Other potential applications, such as cognition or metabolism, are underrepresented with few studies and remain exploratory.

The **strength of the evidence** is notable for **hepatitis B** and **sepsis**, where multiple randomised controlled trials (RCTs) are available. The **ETASS study (2013)** on severe sepsis is the most frequently cited work. Methodological strengths include **multicentric design** and **standardised dosing**. Weaknesses include **heterogeneity of endpoints** (e.g., mortality vs. laboratory parameters) and **combination with other therapies**, which complicates isolated evaluation. Preclinical studies (animal models, cell cultures) provide mechanistic insights but do not establish effects in humans.

4. What Is Often Claimed — and What the Data Support

STATEMENT	STUDY EVIDENCE
Thymosin Alpha-1 in cancer	Controlled studies exist only for metastatic melanoma and liver cancer . The evidence base for other tumour entities is preclinical or observational. Combination
Use in autoimmune diseases	There are no controlled studies on rheumatoid arthritis, multiple sclerosis, or other autoimmune diseases. Preclinical work suggests immunoregulatory effects,
Cognitive effects	Few controlled studies have examined thymosin alpha-1 in cognitive impairment , primarily within the context of hepatitis or chemotherapy. A specific mechanism
Oral bioavailability	All controlled studies utilise parenteral administration (subcutaneous, intravenous). Oral formulations have not been systematically investigated, despite their

5. Profile: Molecule and Charge

Thymosin Alpha-1 is not a single molecule but a **mixture** — there is no molecular formula or fixed molecular mass. What can be described are functional groups, charge behaviour, and redox properties; this is the focus of the next section.

6. Charge, Electrons, Radicals

Thymosin Alpha-1 (Tα1) is an acidic peptide with an isoelectric point of 3.55–4.2, due to a high content of glutamic acid and aspartic acid ^{25 30}. This amino acid composition gives the molecule a negative net charge at physiological pH. Purification of the peptide is achieved, among other methods, by metal chelate chromatography (cation exchange) and cation-exchange chromatography, indicating interactions with positively charged groups ^{24 31}. It also reduces reactive oxygen species (ROS) in human lung epithelial cells and enhances the activity of antioxidant enzymes ^{27 29}. Whether these effects result from direct electron transfer or indirect modulation of redox-sensitive signalling pathways remains to be clarified.

PROVEN Tα1 delays ROS production and glutathione depletion during apoptosis in thymocytes but does not protect against H₂O₂-induced oxidative damage ^{26 28}. This suggests an early intervention in the apoptosis signalling pathway rather than direct radical inactivation. **Plausible:** The ROS reduction observed in cell cultures ^{27 29} may reflect modulation of macrophage activity, as Tα1 increases the release of ROS, nitric oxide (NO), and pro-inflammatory cytokines (IL-1, TNF) in tumour-associated macrophages (TAM). It remains unclear whether the antioxidant effects of Tα1 in vivo are primarily due to direct radical scavenging or regulation of redox-sensitive molecules (e.g., NF-κB, Nrf2). Moreover, measurements of electron transfer properties in humans are lacking. It should be examined whether the IC₅₀ values observed in vitro ^{27 27} are physiologically relevant and whether Tα1 accumulates locally in tissues with high oxidative stress (e.g., sites of inflammation).

7. Interactions with Other Substances

With which other substances on this platform Tα1 has been studied or discussed in human trials and reviews — as combination, comparator, or shared mechanism. The number indicates studies in which both were involved.

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Chronic inflammation	75	22
Stress, cortisol and inflammation	8	1

In controlled human studies, Thymosin Alpha-1 (Tα1) has been investigated in combination with various drugs without documentation of serious interactions. In the treatment of severe sepsis, combination with standard care showed no unexpected adverse events ¹. In metastatic melanoma, Tα1 was combined with dacarbazine and interferon alfa, with the immunomodulatory effect of Tα1 being the focus rather than interactions with co-medications ⁵. Similar combinations were used in chronic hepatitis C (with interferon alfa) ⁶, infections (with carbapenems and ulinastatin) ¹⁰, and non-small cell lung cancer (with cisplatin, etoposide and interferon alfa), again without reports of specific pharmacokinetic or pharmacodynamic interference ^{19 19}.

PLAUSIBLE Combination with immunomodulatory or cytostatic agents (e.g., interferons, nucleoside analogues, HAART) suggests additive or synergistic effects, without evidence of direct enzyme induction (e.g., CYP system) or binding interference. Studies in hepatitis B examined Tα1 with entecavir or lamivudine ²², without documented interactions at absorption or metabolism level. Whether Tα1 affects the bioavailability of other substances remains unclear. Next, it should be examined whether Tα1 alters the expression of transport proteins (e.g., P-glycoprotein) or enzymes relevant to drug metabolism.

8. Overdose, Tolerability, Limits

Proven: Low toxicity and good tolerability of Thymosin Alpha-1 (Tα1) in controlled human studies In several randomised controlled trials in patients with chronic hepatitis B or sepsis, Tα1 showed no treatment-related serious adverse events (^{1, 4, 11, 17}). Tolerability was consistently good, even when combined with interferon-α (IFN-α) or chemotherapeutics such as dacarbazine (DTIC) (^{4, 5}). In a dose-finding study with 0.8 mg and 1.6 mg Tα1, adverse effects occurred similarly in both groups, with no dose-dependent increase (¹¹). Haematotoxicity (grade 3/4) was significantly reduced under Tα1 immunotherapy compared with chemotherapy alone (³²). Studies included long-term use over six months (^{11, 11}), with no cumulative toxicities reported. Contraindications or upper limits were not identified in the studied populations, as even in pre-treated non-responders (e.g., after IFN-α-2b), no increased risks were observed (¹²).

Plausible: Lack of evidence for overdose, but limited data on extreme doses Available studies suggest a wide therapeutic window, as even the highest tested dose of 1.6 mg Tα1 showed no increased toxicity compared with 0.8 mg (^{11, 11}). Systematic investigations of overdoses or acute toxicity limits are, however, lacking. Pharmacokinetics and dosing recommendations have been described in reviews (¹⁶), but without explicit mention of maximum doses or contraindications. Since Tα1 was exclusively used in studies involving hepatitis B patients or oncological cohorts (e.g., metastatic melanoma) (^{5, 17}), it remains unclear whether comorbidities such as severe renal or hepatic insufficiency affect tolerability. Next, it should be examined whether preclinical toxicity studies (animal models) or phase I trials in healthy volunteers define dose upper limits.

9. The Most Robust Studies

Ordered by evidence level, not by prominence. The full evaluation includes significantly more studies; only the most robust are listed here.

Controlled Human Studies

- ¹ The efficacy of thymosin alpha 1 for severe sepsis (ETASS): a multicenter, single-blind, randomized and controlled trial (2013)
- ² Efficacy of thymosin alpha1 in patients with chronic hepatitis B: a randomized, controlled trial (1998)
- ³ Thymosin treatment of chronic hepatitis B: a placebo-controlled pilot trial (1991)
- ⁴ A randomized controlled trial of thymosin-alpha1 versus interferon alfa treatment in patients with hepatitis B e antigen antibody--and hepatitis B ... (1996)
- ⁵ Large randomized study of thymosin alpha 1, interferon alfa, or both in combination with dacarbazine in patients with metastatic melanoma (2010)
- ⁶ Combination therapy with thymosin alpha1 and interferon for the treatment of chronic hepatitis C infection: a randomized, placebo-controlled ... (1998)
- Current therapeutic trends in therapy for chronic viral hepatitis (1997)
- ⁷ Immune enhancement in patients with predicted severe acute necrotising pancreatitis: a multicentre double-blind randomised controlled trial (2022)
- ⁸ Thymosin alpha1 treatment of chronic hepatitis B: results of a phase III multicentre, randomized, double-blind and placebo-controlled study (1999)
- ⁹ The efficacy of thymosin α1 as immunomodulatory treatment for sepsis: a systematic review of randomized controlled trials (2016)
- ¹⁰ Thymosin alpha1- and ulinastatin-based immunomodulatory strategy for sepsis arising from intra-abdominal infection due to carbapenem-resistant ... (2008)
- ¹¹ The efficacy and safety of thymosin alpha-1 in Japanese patients with chronic hepatitis B; results from a randomized clinical trial (2005)
- ¹² Combination low-dose lymphoblastoid interferon and thymosin alpha 1 therapy in the treatment of chronic hepatitis B (1996)
- ¹³ Thymosin alpha1 based immunomodulatory therapy for sepsis: a systematic review and meta-analysis (2015)
- ¹⁴ Ulinastatin and/or thymosin α1 for severe sepsis: A systematic review and meta-analysis (2016)
- ¹⁵ Combination thymosin alpha 1 and lymphoblastoid interferon treatment in chronic hepatitis C (1996)
- ¹⁶ Thymosin alpha-1 (2001)
- ¹⁷ Efficacy of thymosin alpha-1 and interferon alpha in treatment of chronic viral hepatitis B: a randomized controlled study (2006)
- ¹⁸ Combination treatment with zidovudine, thymosin alpha 1 and interferon-alpha in human immunodeficiency virus infection (1994)
- ¹⁹ Sequential chemoimmunotherapy for advanced non-small cell lung cancer using cisplatin, etoposide, thymosin-alpha 1 and interferon-alpha 2a (1995)
- ²⁰ Effect of ulinastatin combined with thymosin alpha1 on sepsis: A systematic review and meta-analysis of Chinese and Indian patients (2017)
- ²¹ A pilot study of the safety and efficacy of thymosin alpha 1 in augmenting immune reconstitution in HIV-infected patients with low CD4 counts taking ... (2003)

- ²² Long-term outcomes of thymosin-alpha 1 and interferon alpha-2b combination therapy in patients with hepatitis B e antigen (HBeAg) negative chronic ... (2003)
- ²³ A randomized, controlled study of thymosin-alpha1 therapy in patients with anti-HBe, HBV-DNA-positive chronic hepatitis B (2000)

10. Summary

What is proven: Thymosin Alpha-1 demonstrates consistent immunomodulatory effects in multiple randomized controlled trials (RCTs), particularly in severe sepsis and chronic hepatitis B. In sepsis, it significantly reduced 28-day mortality (26.0 % vs. 35.0 %) and improved immunological parameters such as HLA-DR expression and SOFA score. In chronic hepatitis B, it led to virological response (HBV-DNA negativity) in up to 14 % of patients (vs. 4 % placebo) and ALT normalization in 36.4 %. Safety and tolerability are well documented, with mild local reactions and transient liver enzyme fluctuations as the most common adverse effects. In oncology (metastatic melanoma), thymosin alpha-1 in combination with chemoimmunotherapy showed higher response rates, though without a significant survival benefit.

What is plausible and what this could imply: **Plausible:** Thymosin Alpha-1 stabilizes immune responses in sepsis by restoring T-cell function and modulating cytokine balance (e.g., TNF- α , IL-6 vs. IL-10). In viral hepatitis, it may enhance antiviral immunity via Toll-like receptors (TLR3/4/9), as suggested by preclinical data. In oncology, observational studies indicate that thymosin alpha-1 improves antitumor immune responses by modulating the tumor microenvironment (e.g., M2 polarization of macrophages). **Hypothesis:** Combination with immune checkpoint inhibitors (ICIs) could yield synergistic effects in solid tumors by overcoming immunosuppressive mechanisms. In COVID-19 and other severe infections, thymosin alpha-1 may reduce T-cell exhaustion, though this has not been systematically investigated. What is missing are studies on optimal dosing, sequencing, and combination with other therapies, as well as long-term effects.

What a study would need to clarify: Systematic gaps remain in the lack of standardized dosing (0.8–6.4 mg) and combination with other therapies (e.g., interferons, chemotherapy). In sepsis, RCTs with stratified analysis by severity or pathogen are lacking to identify subgroups that benefit most from thymosin alpha-1. In viral hepatitis, it is unclear whether it sustainably influences virus elimination or reduces liver fibrosis. In oncology, large randomized trials combining thymosin alpha-1 with immune checkpoint inhibitors are needed to validate synergistic effects. Additionally, pharmacokinetic and pharmacodynamic studies, as well as long-term safety and efficacy data, are lacking. Methodologically, multicentre RCTs with clearly defined endpoints and longer follow-up (e.g., 5-year survival) would be desirable to assess the transferability of predominantly Asian studies to other populations.

11. What Remains Open

- **Long-term safety:** Whether repeated administration of thymosin alpha-1 leads to **autoimmune reactions** or **tolerance development** remains unclear. Existing safety studies cover a maximum of 12 months.
- **Combination therapies:** Most studies combine thymosin alpha-1 with **interferons** or **antiviral agents**. Whether effects are additive, synergistic, or antagonistic has not been systematically investigated.
- **Biomarkers:** There are **no validated biomarkers** to predict response to thymosin alpha-1. Identifying responders would be critical for personalized therapy.

12. Further Paths

Themes, modes of action, and chains in which this substance appears — for those looking beyond the substance itself.

- Interaction network

Topics, mechanisms and chains in which this substance appears — for those who want to look beyond the substance.

Frequently Asked Questions

Why is thymosin alpha-1 not more widely used for viral infections?

Thymosin Alpha-1 is **not a standard therapy**, as the evidence base for many viral infections (e.g., influenza, HIV) remains **limited**. Most controlled trials focus on **hepatitis B/C** and **sepsis**, where it is used as an **add-on therapy**. For other viruses, RCTs demonstrating superiority over established treatments are lacking. Additionally, the **cost-effectiveness** of peptide therapies remains unclear.

Can thymosin alpha-1 enhance vaccine-induced immune responses?

Plausible: Preclinical studies suggest that thymosin alpha-1 may increase **antibody production** following vaccination (e.g., against influenza). A 2011 review discusses its potential as an **adjuvant**, but controlled human studies are still pending. The **question** of whether it improves vaccine responses in immunocompromised individuals (e.g., older adults) remains open and would require RCTs with clear immunological endpoints.

Are there differences between synthetic and natural thymosin alpha-1?

Confirmed: All controlled trials use **synthetic thymosin alpha-1**, which is identical to the natural peptide. Natural extracts from thymus tissue do **not** contain pure thymosin alpha-1 but a mixture of various peptides. The **standardisation** of synthetic preparations enables reproducible dosing, whereas natural extracts vary in composition and have not been systematically studied.

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