Drugs of the Future 2005, 30(10): 1006-1012

CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.10.942815

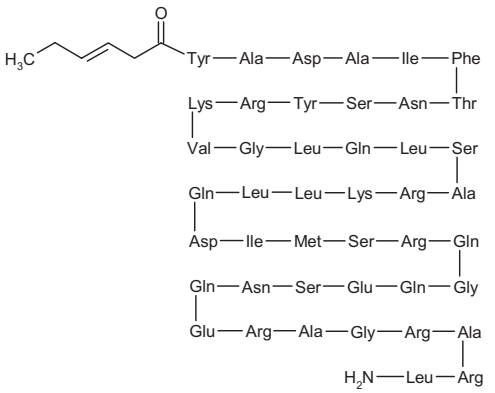
TH-9507

Treatment of AIDS-Associated Lipodystrophy
Treatment of Cachexia
Growth Hormone-Releasing Factor Analogue

ThGRF (1-44)
Hex-hGRF

N-[3(*E*)-Hexenoyl]-L-tyrosyl-L-alanyl-L-aspartyl-L-alanyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-glycyl-L-leucyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-aspartyl-L-isoleucyl-L-methionyl-L-seryl-L-arginyl-L-glutaminyl-glycyl-L-glutaminyl-L-glutamyl-L-seryl-L-asparaginyl-L-glutaminyl-L-glutamyl-L-arginyl-L-alanyl-glycyl-L-arginyl-L-alanyl-L-arginyl-L-leucinamide

N-[1-Oxo-3(*E*)-hexenyl]-somatoliberin (human pancreatic islet)



$C_{221}H_{366}N_{72}O_{67}S$ Mol wt: 5135.7818

CAS: 218949-48-5

EN: 249517

Abstract

Aging and certain diseases such as HIV-related lipodystrophy are associated with reduced levels of growth hormone (GH) and/or insulin-like growth factor-I (IGF-I). Unfortunately, GH injections do not mimic the pulsatile pattern of endogenous GH secretion and are often associated with unwanted effects. Administration of human growth hormone-releasing factor (hGRF) could raise GH levels in a more physiological manner, thereby avoiding unwanted effects but its elimination half-life is short. Researchers have therefore focused on creating GRF analogues for the treatment of GH deficiency. TH-9507 (ThGRF[1-44]) is one such hGRF analogue that exhibits increased stability and half-life. The agent was shown to increase circulating GH and IGF-1 and induce pulsatile GH secretion in preclinical models. TH-9507 has also been shown to be effective in clinical trials in elderly subjects and patients with COPD-related wasting and HIV-associated lipodystrophy, and is in phase II and III development for the treatment of wasting and HIV-associated lipodystrophy, respectively.

Synthesis

TH-9507 can be chemically synthesised by standard solid-phase methodology, using Fmoc-amino acids and Fmoc-Pal-PEG resin for the production of *C*-terminal carboxamides. The hydrophobic tail, 3(*E*)-hexenoic acid can be anchored to the *N*-terminus, after Fmoc deprotection, using 3(*E*)-hexenoic free acid and an active coupling reagent such as benzotriazole-1-yloxytris(dimethylamino)phosphonium hexafluorofosfate (1, 2).

Introduction

Growth hormone (GH) is a peptide hormone that is produced and secreted from the anterior pituitary gland in response to the binding of growth hormone-releasing factor (GRF, GHRF, GHRH), a 44-amino-acid peptide released from the hypothalamus. GH plays an important role in sustaining anabolic integrity in adults, which includes maintaining muscle mass, bone mass and protein synthesis. GH possesses direct lipolytic actions, thus reducing adipose cells, and it stimulates the secretion of insulin-like growth factor-I (IGF-I), a tissue growth factor with anabolic properties, from the liver or locally in peripheral target tissues (3, 4).

Aging and certain diseases such as HIV-related lipodystrophy (which results in fat maldistribution, *i.e.*, visceral adipose tissue [VAT] accumulation and metabolic abnormalities) and type 2 diabetes are associated with reduced levels of GH and/or IGF-I. Reduced levels of GH and/or IGF-I are associated with conditions including muscle wasting, reduced immune response and sleep disturbances, as well as cachexia and muscle wasting in chronic obstructive pulmonary disease (COPD). The administration of GH has been attempted but has shown limited success, does not mimic the pulsatile endogenous GH secretion and can frequently cause unwanted effects (3-14).

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GRF together with the inhibitory peptide somatostatin are responsible for regulating GH secretion in a pulsatile manner. Theoretically, GRF could raise GH levels in a more physiological manner, thus avoiding unwanted effects. However, the elimination half-life of human GRF (hGRF) administered i.v. is about 7 min due to rapid inactivation by plasma dipeptidyl aminopeptidase, which specifically cleaves the Ala2-Asp3 bond. Administration of GRF is therefore not a clinically feasible option (15).

Researchers have thus focused on creating GRF analogues for the treatment of such disorders. TH-9507 (ThGRF[1-44]) is the result of the modification of hGRF involving the addition of a *trans*-hexenyl moiety on the *N*-terminus. The modification resulted in increased stability of the molecule via enhanced resistance to enzyme degradation, and therefore an increased half-life. The agent was shown to increase circulating GH and IGF-I and could also induce pulsatile GH secretion. TH-9507 was therefore chosen for further development as a treatment for conditions associated with reduced GH secretion, including age-related catabolic and metabolic conditions (16-18).

Pharmacological Actions

TH-9507 potently increased GH secretion in a dose-related manner in young growing pigs administrated a single s.c. dose (0.11-3 μg/kg). GH levels were increased (AUC pGH x 8 h = 2640 ± 395 and 6092 ± 962 ng.min/ml at 0.11 and 3 μg/kg, respectively) for at least 8 h. In contrast, higher doses of hGRF(1-44) (3-81 μg/kg) only increased GH (2740 ± 243 and 3663 ± 515 ng.min/ml at 3 and 81 μg/kg, respectively) for about 2-3 h (18).

An *in vivo* study in pigs implanted s.c. with a pure solid TH-9507 (15 mg) implant or a TH-9507/Contramid® (cross-linked high amylose starch) solid implant (15 mg), or injected s.c. with TH-9507 (10 μg/kg b.i.d. for 5 consecutive days), showed that serum IGF-I concentrations increased over 10 days in all implanted animals. An initial IGF-I peak was avoided in the group implanted with TH-9507/Contramid®, but not in the groups treated by s.c. injection or implanted with the pure TH-9507 implant. Moreover, mice implanted with the TH-9507/Contramid® implant did not show any adverse reactions. Thus, TH-9507/Contramid® implants may be an effective way to ensure sustained delivery of TH-9507 (19).

Pharmacokinetics

The elimination half-life of TH-9507 as determined *in vitro* in experiments using fresh human plasma was calculated to be 8.1 h. In contrast, the half-life of hGRF(1-44) in these same experiments was 0.56 h (18).

The pharmacokinetics of inhaled (about 375 μg/kg intratracheal [i.t.] dry powder insufflation), s.c. (about 38 μg/kg) and i.v. (100 μg/kg) TH-9507 were examined in dogs. Bioavailability of the agent following inhalation was 41% relative to s.c. administration; the absolute bioavailability for i.t. TH-9507 was 13%. There were no significant differences in the half-life following i.t. or s.c. dosing (39 and 26 min, respectively), although mean residence time was significantly longer following inhalation (74 min *vs.* 52 min). C_{max} for s.c., i.t. and i.v. TH-9507 was 17 ± 6, 35 ± 10 and 427 ± 118 ng/ml, respectively, and AUC was 604 ± 138, 2617 ± 1036 and 5301 ± 2145 ng.min/ml, respectively. Results suggest that inhalation of TH-9507 may be an effective alternative to s.c. dosing (20).

Toxicity

Results from *in vitro* chromosome aberration (125-2000 μg/ml) and bacterial reverse mutation (up to 5000 μg/plate) assays indicated no clastogenic or mutagenic effects. Similarly, negative results were obtained in an *in vivo* mammalian erythrocyte micronucleus assay in mice (25-100 mg/kg) (21).

The safety of TH-9507 was examined in both acute and subchronic preclinical toxicology studies. Acute administration of the agent at doses of 100 and 200 mg/kg i.v. in rats and mice resulted in severe but transient clinical signs at the lower dose and 70-80% mortality at the higher dose. No toxicity was observed following i.v. administration of TH-9507 of doses up to 100 μg/kg/day for 2 weeks to rats and dogs. Further experiments using rats and dogs showed that administration of TH-9507 at s.c. doses of 100-600 μg/kg/day for 3-4 months resulted in dose-related increases in plasma TH-9507 levels and bioactivity, and increases in body weight gain, food intake, reversible hepatocellular vacuolization and/or reversible increases in phosphorus, triglycerides, cholesterol and proteins were observed; injection-site reactions were seen, but there was no evidence of adverse effects on the CNS or respiratory system (21).

There was no evidence of maternal toxicity, embryonic lethality, fetotoxicity or teratogenicity according to studies performed in rabbits (100-600 μg/kg/day s.c. on gestational days 7-19). Results from s.c. fertility and embryofetal studies in rats showed that TH-9507 (100, 300 or 600 μg/kg/day) had no effect on reproduction in males (treated for at least 28 days prior to mating and throughout) and females (14 days prior to mating, during mating and through gestational day 17). No major external, internal or skeletal abnormalities were observed in the F1 offspring. However, increased fetal weight and advanced ossification were observed at a maternal dose of 600 μg/kg/day (22).

Clinical Studies

The pharmacokinetics, safety and efficacy of TH-9507 (0.5, 1 or 2 mg s.c. once daily for 7 consecutive days) were assessed in 50-60-year-old healthy male volunteers (n=60) in a randomized, double-blind, placebo-controlled trial. C_{max} and AUC values increased proportionally with dose and the half-life of the agent ranged between 2 and 5 h. Administration of TH-9507 resulted in increases in GH and IGF-I that were dose-related up to 1 mg; levels achieved with the 1- and 2-mg doses were similar. IGF-I

levels increased 37%, 89% and 107% over baseline values for the respective TH-9507 doses, compared to 8% for placebo. Mean IGF-I levels obtained with doses of 1 and 2 mg (286 ± 25 and 284 ± 55 ng/ml, respectively) were similar to those obtained in young adults; IGF-I levels at all doses were < 400 ng/ml in all subjects. TH-9507 was specific for GH secretion since prolactin, ACTH (adrenocorticotropic hormone), cortisol, TSH (thyroid-stimulating hormone), LH (luteinizing hormone) and FSH (follicle-stimulating hormone) levels were unaffected by treatment. The only adverse events reported were minor and unrelated to dose, and included headache and injection-site reactions (17).

A randomized, open-label, crossover study was conducted in 12 male and 12 female elderly (mean age = 73 ± 2 years; body mass index [BMI] = 26 ± 2 kg/m^2) healthy subjects to examine the endocrine and metabolic effects of TH-9507 (2 mg s.c. once or twice daily for 14 days). Treatment was well tolerated at both doses and the majority of adverse events reported were mild and resolved spontaneously; no cases of arthralgia were seen. Treatment resulted in significant increases in IGF-I, with significantly greater increases observed with b.i.d. dosing as compared to once-daily dosing (156% *vs.* 110%). No significant gender-related differences in IGF-I increases were observed following b.i.d. dosing, although women were significantly more sensitive to the effects of TH-9507 following once-daily dosing. Once- and twice-daily treatment with TH-9507 also decreased serum LDL cholesterol by 7% and 15%, respectively (23). The results from this study and those that follow are depicted in Table I.

Results from 5 randomized, placebo-controlled trials involving a total of 259 elderly (mean age: 74 ± 5 years), insomniac and diabetic subjects administrated TH-9507 (1 or 2 mg s.c. daily for 1 week to 3 months) examined the influence of gender on IGF-I increases. IGF-I levels of all subjects remained within the physiological range for young subjects throughout the treatment periods. Elderly, diabetic and insomniac women all tended to have lower baseline IGF-I levels as compared to men. Moreover, elderly women were significantly less responsive than elderly men at the lower dose (IGF-1 increase = 23 ± 28 ng/ml *vs.* 54 ± 38 ng/ml), but no gender differences were observed in younger (+91 ± 23 and +92 ± 9 ng/ml, respectively) or elderly subjects (+53 ± 41 and +51 ± 40 ng/ml, respectively) at the higher dose. Similar gender differences were observed in diabetic patients at the lower but not the higher dose (24).

A randomized, double-blind, placebo-controlled study involving 87 elderly (mean age: 74.6 ± 5.8 years; BMI = 27.8 ± 5.4 kg/m^2) healthy subjects examined the effects of TH-9507 (1 or 2 mg s.c. daily for 8 weeks) on immune responses to an influenza vaccination (including Panama, New Caledonia and Victoria inactivated antigens) given at week 4. Eighty-one subjects completed the study, which included a 12-week follow-up period. Of the 7 subjects who discontinued, 6 did so for reasons unrelated to treatment; 1 patient in the higher dose group discontinued due to pain at the injection site. The incidence of adverse events was similar between treatment groups except in the case of injection-site reactions where a dose-related trend was seen; no serious adverse events were reported. Eosinophil counts were higher in the TH-9507 treatment groups as compared to the placebo group, although this was not considered clinically significant. TH-9507 treatment did not affect blood or urine parameters and no anti-TH-9507 antibodies were detected. Influenza-related symptoms developed in all treatment groups with a similar incidence, and influenza-specific antibody titers at week 6 were comparable in all treatment groups. However, significantly more subjects in the higher dose TH-9507 group achieved protective antibody levels (> 1/40) for the Victoria strain as compared to placebo from week 6 to the end of the study period (week 20); no significant differences were observed for the other strains. Subjects treated with TH-9507 exhibited dose-related increases in IGF-I and IGF-binding protein-3 (IGFBP-3) levels that were significantly higher than with placebo throughout the treatment period; IGF-I levels returned to baseline values following cessation of treatment. Moreover, maximal proliferative influenza-specific T-cell responses obtained at week 6 were significantly higher in the 2-mg TH-9507 group. Results suggest that TH-9507 may be effective in conditions where cell-mediated immunity is depressed, such as in the case of viral infections in the elderly, HIV infection and high-dose chemotherapy (25).

A multicenter, randomized, double-blind, placebo-controlled study in 109 men and women (mean age: 64.5 ± 8.2 years) with stable COPD (predicted FEV_1 = 38 ± 13%) and various degrees of wasting (BMI = 14.2-27.4 kg/m^2) examined the anabolic effects and efficacy of TH-9507 (1 or 2 mg s.c. daily for 3 months). Discontinuation rates and the incidence and severity of adverse events were similar for all groups. No clinically significant changes in vital signs or laboratory parameters, including glucose and glycosylated hemoglobin (HbA1c), were seen and no anti-TH-9507 antibodies were detected. Treatment with the agent significantly and dose-dependently increased serum IGF-I levels as compared to placebo (+50% and +92%, respectively, for 1 and 2 mg *vs.* –6% for placebo) and significantly increased lean body mass (0.9-1.3 kg *vs.* –0.1 kg) at 1, 2 and 3 months. Fat mass was significantly decreased in both TH-9507 dose groups at 2 and 3 months. Analysis of functional performance (*i.e.*, exercise duration time [EDT] during a submaximal constant work rate cycle, 6-min walking distance [6-MWD] and isokinetic muscle strength [MS]) revealed a significantly greater overall improvement in MS in the higher dose group for knee extension at 90 degrees and in Borg scores at isotime in EDT for leg and breathing discomfort. No significant differences were observed among groups for the other parameters tested, except for a significantly poorer performance in the 6-MWD in the lower dose group compared to placebo. However, these results probably reflect the greater proportion of patients with severe COPD in this group. No

Table I: Clinical studies of TH-9507 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy elderly volunteers	Randomized Open Crossover	TH-9507, 2 mg s.c. o.d. x 14 d TH-9507, 2 mg s.c. b.i.d. x 14 d	24	TH-9507 increased plasma IGF-I and reduced LDL cholesterol levels in elderly volunteers. Both once- and twice-daily regimens were well tolerated	23
Healthy elderly volunteers, Diabetes, Insomnia	Randomized Pooled/meta-analysis	TH-9507, 1 mg/d s.c. 1 wk - 3 mo TH-9507, 2 mg/d s.c. 1 wk - 3 mo Placebo	259	The effect of gender on the IGF-I response to TH-9507 provided the basis for the use of at least 1 mg in younger or 2 mg in older patients for optimizing therapeutic benefit in both men and women with insomnia and diabetes	24
Healthy elderly volunteers	Randomized Double-blind Multicenter	TH-9507, 1 mg/d s.c. x 8 wks (n=29) TH-9507, 2 mg/d s.c. x 8 wks (n=29) Placebo (n=29)	87	Daily administration of TH-9507 for 8 weeks induced a dose-related increase in IGF-I levels in healthy elderly volunteers	25
Cachexia, Chronic obstructive pulmonary disease	Randomized Double-blind	TH-9507, 1 mg s.c. o.d. x 3 mo TH-9507, 2 mg s.c. o.d. x 3 mo Placebo	109	Compared to placebo, a dose of 2 mg of TH-9507 significantly improved inspiratory muscle strength in patients with wasting and chronic obstructive pulmonary disease but had no effects on expiratory muscle strength. Both TH-9507 doses were well tolerated. Other effects included: improvement in knee extension muscle strength and exercise duration time scores, increase in plasma IGF-I levels and lean body mass, and reduced fat mass	26-28
HIV infection, Lipodystrophy	Randomized Double-blind Multicenter	TH-9507, 1 mg s.c. o.d. x 12 wks (n=19) TH-9507, 2 mg s.c. o.d. x 12 wks (n=21) Placebo (n=21)	61	Once-daily TH-9507 was well tolerated and effective in reducing waist circumference and improving lipid profile in patients with HIV infection and central fat accumulation. TH-9507 also improved the quality of life in HIV-infected patients with abdominal fat accumulation. The benefits of TH-9507 were mainly associated with improvement in enlarged abdominal girth and bloating	29
Diabetes, type 2	Randomized Double-blind Multicenter	TH-9507, 1 mg/d s.c. o.d. x 12 wks (n=18) TH-9507, 2 mg/d s.c. o.d. x 12 wks (n=19) Placebo (n=16)	53	TH-9507 at doses up to 2 mg/d was safe and improved total cholesterol levels. Non-HDL cholesterol was significantly decreased compared to placebo and the repeated administration of TH-9507 did not interfere with overall glycemic control in patients with type 2 diabetes	30, 31
Healthy elderly volunteers, Chronic obstructive pulmonary disease, Diabetes, type 2, HIV infection, Lipodystrophy	Randomized Pooled/meta-analysis	TH-9507, 2 mg o.d. x 3 mo TH-9507, 2 mg b.i.d. x 15 d Placebo	247	TH-9507 given once or twice daily was significantly more effective than placebo in improving the serum lipid profile of healthy elderly volunteers and patients suffering from chronic obstructive pulmonary disease, HIV-associated lipodystrophy or type 2 diabetes	32

significant differences were observed among groups in total scores and 3 subscores (impact, symptoms and activities) from the St. George Respiratory Questionnaire (SGRQ) assessing quality of life (QOL). A significant improvement from baseline to month 3 in the pulmonary muscle function parameter PI_{max} (maximal inspiratory mouth pressure) was observed in the 2-mg and placebo groups but not in the 1-mg group; no significant difference in PE_{max} (maximal expiratory mouth pressure) was observed in any group (26-28).

The efficacy of TH-9507 (1 and 2 mg s.c. once daily for 12 weeks) was demonstrated in a multicenter, randomized, double-blind, placebo-controlled study conducted in 61 HIV-infected patients with abdominal fat accumulation (*i.e.*, increased waist circumference and waist-to-hip ratio). Treatment was generally well tolerated. Thirteen patients discontinued, although rates were similar for the treatment and placebo groups. Treatment resulted in significant dose-related increases in IGF-I (+48% and +65% for 1 and 2 mg, respectively) compared to placebo. A significant reduction in trunk fat was observed in the 2-mg group compared to placebo (–9.2% *vs.* +0.8%). No significant changes in limb or subcutaneous fat (SAT) were observed with treatment. Visceral fat (VAT) tended to decrease in the high-dose TH-9507 group, although this did not reach statistical significance (–15.7% *vs.* –5.4% on placebo). However, lean body mass and the VAT-to-SAT ratio were significantly improved in both TH-9507 treatment groups compared to placebo. Moreover, triglyceride and the cholesterol-to-HDL cholesterol ratio significantly decreased in the high-dose TH-9507 group compared to placebo. Treatment with the agent had no effect on glucose. The study also assessed the effect of TH-9507 on health-related QOL. No significant differences were detected among groups except for slight improvements in the TH-9507 groups for mood and social well-being, although these changes did not reach statistical significance. However, clinically significant improvements were found in the 2-mg group as compared to baseline for enlarged abdominal girth and bloating scores. A significant improvement in abdominal pain and a trend for improvement in abdominal tenderness were observed in the lower dose TH-9507 group only. No significant changes were observed in other disease-specific scores (29).

Because many elderly patients who may benefit from the effect of TH-9507 may have glucose intolerance and overt diabetes, a randomized, double-blind, placebo-controlled trial was performed to determine the safety and effects of TH-9507 (1 and 2 mg s.c. daily for 12 weeks) in this patient population. The 53 patients included in the study were on stable antidiabetic regimens (*i.e.*, oral hypoglycemics with or without insulin). Treatment was well tolerated. Adverse event rates were similar in all groups (39%, 58% and 50%, respectively, for 1 and 2 mg TH-9507 and placebo). IGF-I levels increased in a dose-related manner in the TH-9507 dose groups (32% and 67%, respectively, *vs.* 0% on placebo at week 12). There was no significant difference among groups in the insulin response to an oral glucose tolerance test (OGTT), fasting glucose and overall diabetes control. HbA1c levels at week 12 tended to decrease in the placebo and 1-mg TH-9507 groups, but remained unchanged in the 2-mg TH-9507 group. The incidence of clinically relevant changes in antidiabetic medication was similar in both treatment and placebo groups. No patients were discontinued or rated as worse in terms of glucose control. A significant decrease in total cholesterol was observed in the 2-mg group (–6% *vs.* +5% and +3% on placebo and 1 mg TH-9507, respectively) at week 12 and this decrease was due to a reduction in non-HDL cholesterol levels; there were no changes in HDL cholesterol or triglyceride levels. Thus, repeated TH-9507 administration had no effect on glucose tolerance, insulin response or glycemic control and therefore can be safely used in patients with type 2 diabetes (30, 31).

Another study analyzed the results of 5 of the above randomized clinical studies involving healthy elderly subjects (n=24), patients with COPD (n=109), patients with type 2 diabetes (n=53) and patients with HIV-associated lipodystrophy (n=61) to determine the effects of TH-9507 on serum lipid parameters. Results revealed that in elderly subjects, treatment with the agent at 2 mg b.i.d. for 15 days significantly decreased total cholesterol and LDL cholesterol as compared to baseline values. Treatment of patients with COPD with 2 mg once daily was also associated with a significant decrease in total cholesterol and LDL cholesterol as compared to baseline, and treatment of subjects with type 2 diabetes with the same dose for 12 weeks resulted in significant reductions in total cholesterol and non-HDL cholesterol. Moreover, treatment of HIV-infected patients with abdominal fat accumulation with a dose of 2 mg for 12 weeks resulted in a significant reduction in triglycerides and an improvement in the total cholesterol-to-HDL cholesterol ratio. From these results, it was concluded that TH-9507 has a beneficial effect on the atherogenic lipid profile and may therefore be effective in conditions associated with increased cardiovascular risk, such as HIV lipodystrophy and metabolic syndrome (32).

TH-9507 continues to undergo active phase II and phase III testing for the treatment of wasting and HIV-associated lipodystrophy, respectively. A randomized, double-blind, placebo-controlled study is currently under way to further examine the safety and efficacy of 2 mg TH-9507 for 12 weeks in a larger population of HIV-infected patients with excess abdominal fat accumulation (33-35).

Source

Theratechnologies, Inc. (CA).

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