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Thyrotropin-releasing Hormone Can Relieve Cancer-related Fatigue: Hypothesis and Preliminary Observations

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Fatigue in cancer patients is highly prevalent, predominantly idiopathic, difficult to manage, and has a significant negative impact on quality of life. Thyrotropin-releasing hormone (TRH) exerts normotrophic, state-dependent therapeutic effects in a variety of experimental and clinical situations. To evaluate TRH as a treatment for cancer-related fatigue, an ongoing randomized, placebo-controlled, crossover pilot study of breast cancer patients has been initiated and this report presents preliminary observations conducted with three of these

patients over 4 consecutive weeks, thereby involving a total of six TRH treatments and six saline controls. Global assessment using both subjective and objective parameters showed that TRH exerted clear anti-fatigue effects in four of the six TRH treatments. These responses were rapid in onset and persisted through the 24 h observation period. No anti-fatigue responses were seen in five of the six saline controls. No unexpected side-effects were seen with TRH administration. These initial findings support the proposal that TRH can ameliorate cancer-related fatigue.

KEY WORDS: THYROTROPIN-RELEASING HORMONE; CANCER-RELATED FATIGUE; BREAST CANCER; HOMEOSTASIS

Introduction

Fatigue is the most common symptom of cancer and cancer treatments.¹ It is exceedingly debilitating and may persist for months or even years after completion of treatment.² Frequently accompanied by comorbidities, such as depression or pain, cancer-related fatigue is sometimes associated with underlying contributory factors such as anemia, electrolyte abnormalities or hypothyroidism.³ In most patients, however, specific causative factors

cannot be identified. This idiopathic fatigue is often profound, persistent and invariably unrelieved by rest.⁴ To date, no therapeutic intervention has been shown to be reliably effective.⁵

Cancer-related fatigue can be viewed as a failure of homeostasis. It has been associated with a cascade of interrelated changes in the neuroendocrine system, central/peripheral nervous system, neurotransmitter metabolism and circadian rhythms.^{6,7} Additionally, existing evidence suggests that

fatigue in cancer patients is associated with immune dysfunction and may be due to the actions of various pro-inflammatory cytokines released as a result of the disease process as well as in response to radiation and/or chemotherapeutic treatment interventions.⁸

As first proposed in 2003, thyrotropin-releasing hormone (TRH; pGlu-His-ProNH₂) is thought to be widely involved in the control of behavioral, metabolic and immunological homeostasis.⁹⁻¹¹ This teleologically-based understanding of the fundamental role of TRH is consonant with its ubiquitous distribution and its involvement in many physiological processes, above and beyond its neuroendocrine functions.⁹ Moreover, this unifying hypothesis provides insight into the basis of the widely reported, diverse and non-disease-specific therapeutic effects of TRH and TRH-mimetic analogs.¹⁰ Thus, in various clinical situations and disease states TRH agonism exerts normotrophic, state-dependent therapeutic effects which manifest as restorations of homeostasis, including that of the immune system.¹¹ In instances of behavioral depression, TRH agonism exerts arousing and analeptic actions. Additionally, TRH can counteract various immune dysfunctions known to be associated with cancer-related fatigue.¹¹

In light of the above considerations, it was hypothesized that TRH agonism should ameliorate cancer-related fatigue.¹¹ To assess this possibility, a pilot trial has been set up to examine the effects of TRH on fatigue in breast cancer patients.

Patients and methods

PATIENT CHARACTERISTICS

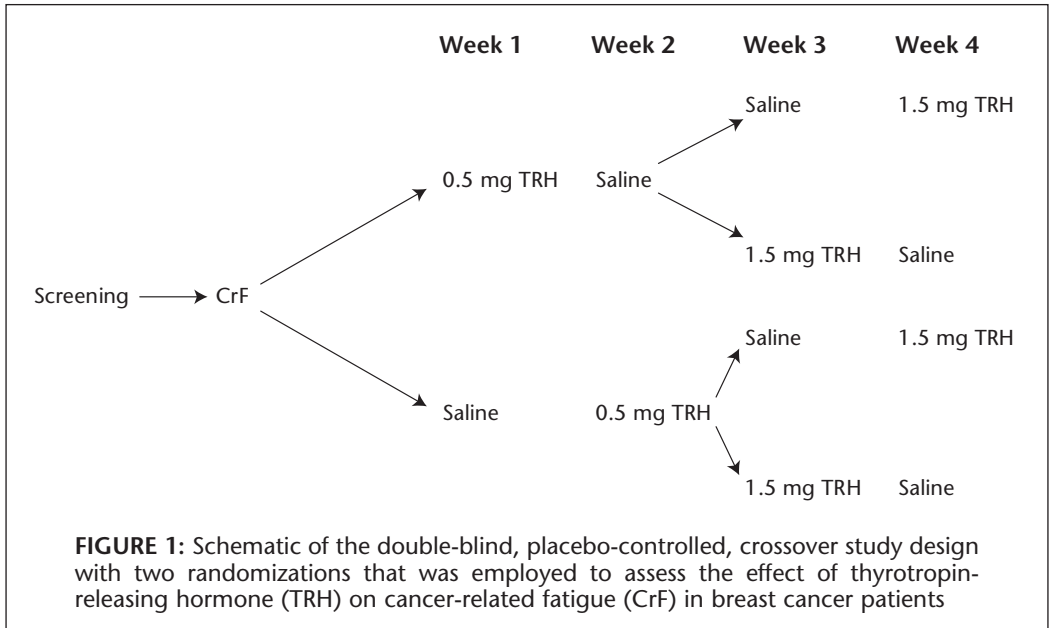
Informed consent was obtained in writing from each participant. Patients with breast cancer who were experiencing cancer-related

fatigue according to the criteria of the International Classification of Diseases 10th Revision (ICD-10)^{12,13} were eligible for inclusion in the study. Patients were also required to have a score of < 34 on the Functional Assessment of Cancer Therapy (FACT)-Fatigue scale¹⁴ at the initial evaluation. Patients with clearly identifiable but untreated causes of fatigue (e.g. anemia) were excluded, as were patients with any unstable and clinically significant psychiatric or substance use disorders, and those with a history of cardiovascular disease. Patients with comorbidities (e.g. depression, insomnia) were included if the comorbid factors were not judged to be the main causative factors of fatigue.

STUDY DESIGN

This pilot phase II trial employed a double-blind, placebo-controlled, crossover design with two randomizations (www.ClinicalTrials.gov identifier NCT00790296). Patients were assessed for fatigue 1 h before and 3, 7, and 24 h after intravenous administration of TRH (either 0.5 or 1.5 mg) or saline placebo. This procedure was performed once weekly over 4 consecutive weeks, resulting in a total of six TRH treatments and six controls (Fig. 1).

The primary outcome measure was the visual analog scale for energy level (VAS-E)¹⁴ as assessed by the subject. Other outcome measures included the multidimensional fatigue inventory,¹⁵ functional assessment using a 6-min walk test¹⁶ and a quality of life assessment using the FACT-General questionnaire.¹⁷ Comorbid factors were evaluated using the modified, four-item Leeds Sleep Evaluation Questionnaire,¹⁸ the Hospital Anxiety and Depression questionnaire¹⁹ and the 65-item Profile of Mood States questionnaire.²⁰ A blinded clinician rated fatigue status and general quality of life using the Clinical Global



Impression (CGI) scale before and after administration of study medication.

The study protocol was approved by the University of Connecticut Health Center Institutional Review Board. All study procedures were conducted in accordance with an Investigational New Drug application (IND 72,351) approved by the Food and Drug Administration of the USA.

Results

To date, three patients have each received two injections of saline and two injections of TRH (0.5 and 1.5 mg) in accordance with the crossover study treatment schedule, giving a total of six TRH treatments and six controls. All three patients were in remission and had completed cancer treatments at least 2 years (range 2 – 5 years) before the study. No clinically relevant medical or psychiatric comorbidities were noted in any of the patients.

Data on the overall positive (+) anti-fatigue or negative (–) no anti-fatigue responses to each of the six TRH treatments

and six controls are presented in Table 1. This shows the combined assessments of the subjective primary outcome measure (VAS-E score) plus the objective walking test results and observations by an observer blinded to the treatments and represent our qualitative global assessments of each patient's response to each treatment. The change in VAS-E scores at 3, 7, and 24 h show that the anti-fatigue related effects of TRH remained evident through the 24 h observation period after dosing (Table 1).

In four of the six TRH treatments, clear anti-fatigue responses were seen. These responses became evident 3 – 7 h after dosing, persisted through the 24 h observation period and were reported as considerable and robust by the patients. Possible dose–response effects of TRH were not evident in these limited data. In patient II with treatment 3 (week 3), no response to TRH was seen, however, at that time the patient was not clearly fatigued, which conceivably might be ascribed to a carry-over effect from the TRH treatment received a

TABLE 1:
Changes in visual analog scale for energy (VAS-E) scores at 3, 7, and 24 h and global assessment of the effect of thyrotropin-releasing hormone (TRH) or saline control on cancer-related fatigue in three breast cancer patients

Patient/Assessment	Treatment/Week			
	1	2	3	4
Patient I	TRH 0.5 mg	Saline ^a	TRH 1.5 mg	Saline ^a
Change in VAS-E ^c				
3 h	+/-	-	+/-	-
7 h	+	-	+	-
24 h	+	-	+	-
Global^d	+	-	+	-
Patient II	Saline	TRH 0.5 mg	TRH 1.5 mg ^b	Saline
Change in VAS-E ^c				
3 h	-	+/-	-	-
7 h	-	+	-	-
24 h	+/-	+	-	+
Global^d	-	+	-	+/-
Patient III	TRH 0.5 mg	Saline	Saline	TRH 1.5 mg
Change in VAS-E ^c				
3 h	+	+	-	+
7 h	+	+	-	+
24 h	+	+	-	+
Global^d	+/-	+	-	+

^aModest increase in fatigue noted.

^bIn this patient no fatigue was evident in week 3 at baseline perhaps as a consequence of previous TRH exposure at week 2.

^cChange in VAS-E was calculated by comparing scores to baseline (1 h prior to study medication administration) and was considered a positive anti-fatigue response (+) if the change in VAS-E score was $\geq 25\%$ compared with baseline; -, no change from baseline; +/-, $< 25\%$ change from baseline.

^dGlobal assessment of the response represents the combined assessments of the subjective visual analog scale for energy level (VAS-E) scores 3, 7, and 24 h after treatment compared with the 1 h pre-treatment baseline and patient comments plus the objective walk test results and the observations of an observer blinded to the treatments: +, overall positive anti-fatigue response, including $\geq 25\%$ increase in VAS-E score compared with baseline; -, no anti-fatigue response; +/-, equivocal, unclear response, including slight increase in VAS-E score.

week earlier. In patient III with treatment 1 (week 1), only a tendency (+/-) towards improvement was discerned after administration of 0.5 mg TRH. Transient, modest increases in blood pressure and heart rate were the main (and expected) side-effects²¹ after TRH administration. No unexpected side-effects were noted.

Among the six placebo infusion trials, a clear anti-fatigue response was noted only in patient III with treatment 2 (week 2). For another placebo infusion trial, no clear

conclusions could be adduced from patient II with treatment 4 (week 4). Saline injections produced no anti-fatigue effects in the other four placebo infusion trials.

Discussion

Despite the widely documented high prevalence of cancer-related fatigue and its impact on quality of life, effective interventions for this debilitating condition remain elusive.⁴ Evidence for non-pharmacological relief of cancer-related

fatigue is largely idiosyncratic and anecdotal.²² Pharmacological interventions, as judged by recent trials with stimulants, have failed to show efficacy in randomized, placebo-controlled studies.^{23–27}

The present data show that TRH had a positive effect on the global assessment of fatigue in three breast cancer patients. Overall, predicted responses (i.e. positive anti-fatigue effects in response to TRH or no response to saline or to TRH in a non-fatigued state) were noted in nine (75%) of the 12 tests, equivocal responses were seen in two and one clear, not-predicted anti-fatigue placebo response was observed. Of note, TRH, like other bioactive neuropeptides, is known to have a plasma half-life of only a few minutes,¹¹ yet the anti-fatigue related effects remained evident through the 24 h observation period after dosing in the present study. The basis for this apparent pharmacokinetic–pharmacodynamic discordance is not understood; however, it should be noted that long term effects of TRH administration have been seen in other studies. Specific examples include electroencephalographic changes observed with TRH administration lasting 24 h²⁸ and anti-fatigue effects of TRH administration lasting 24 h or longer in a study conducted in patients with bipolar depression.²⁹ Although preliminary and limited, these observations are consistent with the hypothesis that TRH

can relieve fatigue in cancer patients. Furthermore, these apparent therapeutic effects can be understood in the context of the normotrophic, homeostasis-promoting actions of TRH agonism^{9–11} and may relate to interactions of TRH with pro-inflammatory cytokines.¹¹

Clearly, more data are needed to substantiate these findings and mechanistic speculations. Nonetheless, they may portend significant medical benefit. Enrolment in the present study is continuing and it is hoped that others will endeavour to evaluate and extend these observations.

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Conflicts of interest

GGY, AJP Jr, and AW are members of TRH Therapeutics LLC, an Oregon-based consulting organization which holds a USA patent (# 7,462,595) on the use of TRH and related peptidomimetics to relieve cancer-related fatigue.

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References

- 1 Hofman M, Ryan JL, Figueroa-Moseley CD, *et al*: Cancer-related fatigue: the scale of the problem. *Oncologist* 2007; **12**(suppl 1): 4–10.
- 2 Bower JE, Ganz PA, Desmond KA, *et al*: Fatigue in long-term breast cancer survivors: a longitudinal investigation. *Cancer* 2006; **106**: 751–758.
- 3 Mock V, Atkinson A, Barsevick A, *et al*: NCCN practice guidelines for cancer-related fatigue. *Oncology (Williston Park)* 2000; **14**: 151–161.
- 4 Stone PC, Minton O: Cancer-related fatigue. *Eur J Cancer* 2008; **44**: 1097–1104.
- 5 Carroll JK, Kohli S, Mustian KM, *et al*: Pharmacological treatment of cancer-related fatigue. *Oncologist* 2007; **12**(suppl 1): 43–51.
- 6 Miller AH, Ancoli-Israel S, Bower JE, *et al*: Neuroendocrine-immune mechanisms of

- behavioural comorbidities in patients with cancer. *J Clin Oncol* 2008; **26**: 971 – 982.
- 7 Payne JK: A neuroendocrine-based regulatory fatigue model. *Biol Res Nurs* 2004; **6**: 141 – 150.
- 8 Schubert C, Hong S, Natarajan L, et al: The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun* 2007; **21**: 413 – 417.
- 9 Gary KA, Sevarino KA, Yarbrough GG, et al: The thyrotropin-releasing hormone (TRH) hypothesis of homeostatic regulation: implications for TRH-based therapeutics. *J Pharmacol Exp Ther* 2003; **305**: 410 – 416.
- 10 Yarbrough GG, Kamath J, Winokur A, et al: Thyrotropin-releasing hormone (TRH) in the neuroaxis: therapeutic effects reflect physiological functions and molecular actions. *Med Hypotheses* 2007; **69**: 1249 – 1256.
- 11 Kamath J, Yarbrough GG, Prange AJ, et al: The thyrotropin-releasing hormone (TRH)-immune system homeostatic hypothesis. *Pharmacol Ther* 2009; **21**: 20 – 28.
- 12 Portenoy RK, Itri LM: Cancer-related fatigue: guidelines for evaluation and management. *Oncologist* 1999; **4**: 1 – 10.
- 13 World Health Organization (WHO): *International Classification of Diseases 10th Revision (ICD-10)*. Geneva: WHO, 1997 (updates to 2008) (available at <http://www.who.int/classifications/icd/en>).
- 14 Van Belle S, Paridaens R, Evers G, et al: Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: proposal for use as a screening tool. *Support Care Cancer* 2005; **13**: 246 – 254.
- 15 Smets EM, Garssen B, Bonke B, et al: The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosomat Res* 1995; **39**: 315 – 325.
- 16 Enright PL: The six-minute walk test. *Respir Care* 2003; **48**: 783 – 785.
- 17 Cella DF, Tulsy DS, Gray G, et al: The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993; **11**: 570 – 579.
- 18 Parrott AC, Hindmarch I: The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigation – a review. *Psychopharmacology* 1980; **71**: 173 – 179.
- 19 Zigmond AS, Snaith RP: The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361 – 370.
- 20 McNair DM, Lorr M, Droppleman LF: *Manual: Profile of Mood States*. San Diego: Educational and Industrial Testing Service, 1981.
- 21 Mellow AM, Sunderland T, Cohen RM, et al: Acute effects of high-dose thyrotropin-releasing hormone infusions in Alzheimer's disease. *Psychopharmacology* 1989; **98**: 403 – 407.
- 22 Markes M, Brockow T, Resch KL: Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev* 2006; **18**: CD005001.
- 23 Mar Fan HG, Clemons M, Xu W, et al: A randomized, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. *Support Care Cancer* 2008; **16**: 577 – 583.
- 24 Bruera E, Valero V, Driver L, et al: Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol* 2006; **24**: 2073 – 2078.
- 25 Butler JM Jr, Case LD, Atkins J, et al: A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. *Int J Radiat Oncol Biol Phys* 2007; **69**: 1496 – 1501.
- 26 Roscoe JA, Morrow GR, Hickok JT, et al: Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res Treat* 2005; **89**: 243 – 249.
- 27 Bruera E, El Osta B, Valero V, et al: Donepezil for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol* 2007; **25**: 3475 – 3481.
- 28 Itil TM, Patterson CD, Polvan N, et al: Clinical and CNS effects of oral and I.V. thyrotropin-releasing hormone in depressed patients. *Dis Nerv Syst* 1975; **36**: 529 – 536.
- 29 Szuba MP, Amsterdam JD, Fernando III AT, et al: Rapid antidepressant response after nocturnal TRH administration in patients with bipolar type I and bipolar type II major depression. *J Clin Psychopharmacol* 2005; **25**: 325 – 330.

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