

Novel Recombinant Human Thyroid-stimulating Hormone in Aiding Post-operative Assessment of Patients With Differentiated Thyroid Cancer—Phase I/II Study

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Abstract

Purpose Thyroid hormone withdrawal (THW) inevitably induced hypothyroidism in patients with differentiated thyroid cancer (DTC), we aimed to evaluate the safety and efficacy of a novel recombinant human thyroid-stimulating hormone (rhTSH, ZGrhTSH) as an alternative of THW in China.

Methods Totally, 64 DTC patients were enrolled with 24 in the dose-escalation cohort equally grouped into 0.9 mg×1d, 0.9 mg×2d, 1.8 mg×1d and 1.8 mg×2d dosage, and 40 further enrolled into 0.9 mg×2d dose-expansion cohort. All patients underwent both ZGrhTSH phase and levothyroxine (L-T₄) withdrawal phase for self-comparison in terms of TSH levels, the radioactive iodine (RAI) uptake, stimulated thyroglobulin level, and the quality of life (QoL).

Results In ZGrhTSH phase, no major serious adverse events was observed, mild symptom of headache was observed in 6.3%, lethargy in 4.7%, asthenia in 3.1% of the patients, and mostly resolved spontaneously within 2 days. Concordant RAI uptake was noticed in 89.1% (57/64) of the patients between ZGrhTSH and L-T₄ withdrawal phases. The concordant thyroglobulin level with a cut-off of 1 mg/L was noticed in 84.7% (50/59) of the patients without the interference of anti-thyroglobulin antibody. The QoL was far better during ZGrhTSH phase than L-T₄ withdrawal phase, with lower Billewicz (-51.30±4.70 vs. -39.10±16.61, P<0.001) and POMS (91.70±16.70 vs. 100.40±22.11, P=0.011) scores which indicate the lower the better. Serum TSH level rose from basal 0.11±0.12 mU/L to a peak of 122.11±42.44 mU/L 24h after the last dose of ZGrhTSH. In L-T₄ withdrawal phase, a median of 23 days after L-T₄ withdrawal was needed, with the mean TSH level of 82.20±31.37 mU/L. The half-life for ZGrhTSH clearance was about 20h.

Conclusion The ZGrhTSH held the promise to be a safe and effective modality in facilitating RAI uptake and serum thyroglobulin stimulation, with better QoL of patients with DTC compared with L-T₄ withdrawal.

Introduction

According to the data of International Agency for Research on Cancer (IARC) in 2020, the new cases of thyroid cancer in China (221,093) accounted for more than one-third of the global number, indicating the relatively high thyroid cancer burden in terms of incidence in China [1, 2]. Differentiated thyroid cancer (DTC) accounts for over 94% of thyroid cancer [3]. Successful management of DTC is based on total thyroidectomy followed by selective radioactive iodine (RAI) ablation and thyroxine therapy for thyroid-stimulating hormone (TSH) suppression. Notably, though a more than 98% of 5-years survival rate revealed by Surveillance, Epidemiology and End Results (SEER) database [4], it was only 84.3% indicating the less favorable survival status in China [5], and urging the need of strengthening thyroid cancer management, particularly a more comprehensive assessment in active surveillance of recurrence and more accurate subsequent therapeutic tailoring such as RAI therapy. During the pre-RAI assessment and active surveillance, diagnostic ¹³¹I-whole body scan (Dx-WBS) and serum stimulated thyroglobulin (s-Tg)

commonly require high TSH stimulation by means such as temporary thyroid hormone withdrawal (THW) for better detection of residual or functional DTC lesions [6–8]. However, during THW period, patients would inevitably experience symptomatic hypothyroidism, of note, in those with the high tumor burden, an adequate TSH stimulation might not be reached due to the exotic tumorigenic thyroid hormone excretion, or even risk to stimulate the tumor growth and cause disease progression, which all may prevent the patients from optimal assessment.

Thyrogen®, a kind of recombinant human TSH (rhTSH), has been approved by Food and Drug Administration (FDA) in 1998, is an exogenous TSH, which can stimulate thyroid cells without THW and has been recommended as an alternative for the preparation of RAI ablation for over 20 years. As a replacement of THW prior to ¹³¹I-WBS or s-Tg examination, rhTSH utilization greatly reduce the suffering of patients during RAI ablation or assessment [9–11]. However, so far rhTSH remains unavailable in China where THW is the only modality for TSH stimulation. The preclinical studies showed that ZGrhTSH, a Chinese rhTSH analog, could bind to TSHR on the cell surface and result in rising of intracellular second messenger cyclic adenosine monophosphate (cAMP), which indicated its biological activity was similar to Thyrogen®. The current phase I and II self-control study was designed to assess the safety, tolerance, and efficacy of ZGrhTSH in diagnostic evaluation and its impact on patient's quality of life (QoL) in comparison with levothyroxine (L-T₄) withdrawal.

Materials And Methods

The study was registered at ClinicalTrials.gov (NCT04137185) and approved by the ethical board of each participated clinical institution. All patients were fully informed and provided written informed consent before enrollment.

Study participants

From May, 2019 to April, 2021, Patients underwent total thyroidectomy and pathologically diagnosed as DTC were enrolled. All the following inclusion criteria should be met: (i) aged 18~75 years; (ii) Dx-WBS planned for the disease status evaluation postoperatively or after initial therapy;(iii) the serum TSH level was controlled below 0.5 mU/L before enrollment;(iv) low-iodine preparation for more than 4 weeks before enrollment. Patients who were pregnant, lactating or not suitable for L-T₄ withdrawal were excluded.

rhTSH

ZGrhTSH was produced by Suzhou Zelgen biopharmaceutical Co., Ltd., with a specification of 1.1 mg per piece. The storage condition should be 2 ~ 8 °C. ZGrhTSH is a hTSH produced by recombinant DNA technology. rhTSH freeze-dried is made from Chinese hamster ovary (CHO) cells that efficiently express hTSH α and β subunit genes, after cell culture, isolation and high purification.

Study design

In this phase I/II, open-label, multicenter self-control study, we evaluated the safety and efficacy of ZGrhTSH in patients with DTC who had referred for postoperative assessment including primarily Dx-WBS and s-Tg. The study consisted of the following I and II parts: dose-escalation (phase I) and dose-expansion (phase II). A total of 64 eligible patients were enrolled with 24 for phase I and followed by 40 for phase II study (Fig. 1). Patients in phase I (n=24) were equally grouped into 0.9 mg×1d, 0.9 mg×2d, 1.8 mg×1d, and 1.8 mg×2d dose regimen sequentially. During phase II study, the dose escalation allowed to initiate only after the safety was confirmed in the prior lower dose regimen. Similar as Thyrogen®, based upon the results of phase I study, 0.9 mg×2d was selected for further phase II study. Pharmacokinetic analysis was performed in all patients of phase I and first 10 patients of phase II.

For each enrolled patient, two phases of ZGrhTSH and L-T₄ withdrawal were successively underwent to compare the influence on elevated TSH level, RAI uptake, Tg secretion, as well as QoL. In ZGrhTSH phase, ZGrhTSH was injected intramuscularly with dosage of the corresponding dose group. In L-T₄ withdrawal phase, the L-T₄ withdrawal was conducted to raise TSH above 30mU/L.

Anti-TSH antibody testing

The presence of antibodies against rhTSH in human serum samples are detected by the typical bridging assay on the MESO Scale Discovery (MSD) platform. Briefly speaking, biotinylated-rhTSH (Bio-rhTSH) and ruthenylated-rhTSH (Ru-rhTSH) are added to human serum samples to form an antibody-drug complex with ADA in the samples during incubation. The complex is then captured and detected on the MSD plate with Streptavidin pre-coated.

Safety assessment

Adverse events (AEs) were observed and documented for all patients during the study. Common terminology criteria for adverse events (CTCAE) version 4.03 was used to evaluate the severity of AEs.

Dx-WBS imaging and interpretation

Each patient was instructed to oral ¹³¹I (74-148 MBq) for Dx-WBS after 24 hours of the last ZGrhTSH injection and after at least two weeks of discontinuation of L-T₄ for ZGrhTSH and L-T₄ withdrawal phase respectively. TSH level ≥30 mU/L and low-iodine diet for more than 4 weeks were required in all patients before oral ¹³¹I administration. Dx-WBS was performed after 48 hours of ¹³¹I administration.

Each Dx-WBS was interpreted independently by two reviewers who didn't identify the patient information about the center, sequence of the scans, the Tg levels, or the surgery condition. The scans were defined as either positive when showing the ¹³¹I concentration in the thyroid bed or abnormal uptake in the neck, the lungs or other extrathyroidal sites, or negative when no ¹³¹I uptake in the thyroid bed or extrathyroidal sites. The locations of the ¹³¹I uptake were compared within each pair of scans to assess whether the two scans were concordant.

Serum measurements

Serum TSH, Tg and anti-Tg antibody (TgAb) levels were measured upon baseline (TSH \leq 0.5 mU/L) and prior to each Dx-WBS (TSH \geq 30 mU/L). For pharmacokinetic analysis, serum samples were obtained at 30min before and 1h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, 72h, 96h, 120h after ZGrhTSH administration. TSH was tested by laboratories of local sites using standard method. Tg and TgAb were tested by central laboratory using electrochemiluminescence method. The measurable range of Tg and TgAb were 0.1-5000.00 μ g/L and 10.00-4000 kU/L, respectively, and a reference range of TgAb for normal value was $<$ 115 kU/L.

Hypothyroid symptoms and QoL measurements

Hypothyroid symptoms were assessed with the Billewicz Scale (score range: -53 ~ 72), which is an international standard for hypothyroidism evaluation, with higher score indicates more obvious hypothyroid symptoms. The QoL was evaluated by the short-form Profile of Mood States (POMS) (score range: 56 ~ 216). Similarly, the higher POMS score suggests the more negative emotional state. The Billewicz Scale and POMS were tested in all patients at the baseline, 1 day before 131 I administration and 3 days after 131 I administration for both ZGrhTSH and L-T₄ withdrawal phases.

Statistical analysis

All efficacy outcomes were assessed in the intention-to-treat population. Proportions were presented with a two-sided 95% CI using Clopper-Pearson method. Comparison of the concordant rate of RAI uptake between ZGrhTSH and L-T₄ withdrawal phases was performed using the McNemar chi-square test. The differences of serum TSH, Tg levels, Hypothyroid symptoms on the Billewicz Scale and QoL on the short-form POMS were analyzed by the Wilcoxon signed-rank test. All statistical analysis were performed in two-side model using SAS 9.4. All safety analyses were made in the population received any dose of ZGrhTSH.

Results

Patient characteristics

Between Apr. 10, 2019 and Nov. 15, 2020, 64 patients (intention-to-treat) were enrolled (Table 1; Fig. 1). There were 18 males (28.1%) and 46 females (71.9%). The median age was 40.0 years (range: 20 to 66 years). Ethnic groups were all Asian (64 cases, 100.0%) and Han. The pathology of all these patients was papillary thyroid cancer.

Table 1
 Characteristics of patients enrolled in this study.

	0.9 mg×1d (N=6)	0.9 mg*2d (N=46)	1.8 mg*1d (N=6)	1.8 mg*2d (N=6)	total (N=64)
Gender					
<i>Male</i>	1	15	1	1	18 (28.1)
<i>Female</i>	5	31	5	5	46 (71.9)
Age, years					
<i>Median</i>	46.5	38.5	41	39.5	40
<i>Range</i>	36,56	20,66	31,54	32,53	20,66
T stage					
<i>T1</i>	3	28	5	4	40(62.5)
<i>T2</i>	0	6	0	1	7(10.9)
<i>T3</i>	1	4	0	1	6(9.4)
<i>T4</i>	2	7	1	0	10(15.6)
<i>unknown</i>	0	1	0	0	1(1.6)
N stage					
<i>N0</i>	1	8	2	0	11(17.2)
<i>N1</i>	5	37	4	6	52(81.3)
<i>unknown</i>	0	1	0	0	1(1.6)
M stage					
<i>M0</i>	6	45	6	6	63(98.4)
<i>M1</i>	0	0	0	0	0(0)
<i>unknown</i>	0	1	0	0	1(1.6)
Stage					
<i>I</i>	4	43	6	6	59(92.2)
<i>II</i>	2	2	0	0	4(6.3)
<i>unknown</i>	0	1	0	0	1(1.6)
Risk Stratification					
<i>low</i>	2	4	1	2	9(14.1)

	0.9 mg×1d (N=6)	0.9 mg*2d (N=46)	1.8 mg*1d (N=6)	1.8 mg*2d (N=6)	total (N=64)
<i>intermediate</i>	1	31	4	4	40(62.5)
<i>high</i>	3	10	1	0	14(21.9)
<i>unknown</i>	0	1	0	0	1(1.6)

Immunogenicity

With available samples in 39 patients, none of them had detectable serum anti-ZGrhTSH antibodies (ADA).

Adverse events

Of the 64 patients enrolled in the study, AEs were observed in 36 (56.3%) patients during ZGrhTSH phase, of which 13 were identified to be related to ZGrhTSH, but usually mild and resolved within 2 days. The most common AE related to ZGrhTSH was headache, which occurred in 4 patients (6.3%). Other AEs included lethargy (4.7%), asthenia (3.1%), etc. ZGrhTSH related AEs were listed in Table 2. No grade 2 and above AEs were observed in ZGrhTSH phase.

Table 2
Adverse events related to ZGrhTSH in the study.

Adverse Events	0.9 mg×1 d (N=6)	0.9 mg×2 d (N=46)	1.8 mg×1 d (N=6)	1.8 mg×2 d (N=6)	Total (N=64)
Nervous system disorders	3 (50.0)	5 (10.9)	1 (16.7)	0	9 (14.1)
<i>Headache</i>	3 (50.0)	0	1 (16.7)	0	4 (6.3)
<i>Lethargy</i>	0	3 (6.5)	0	0	3 (4.7)
<i>Dizziness</i>	0	1 (2.2)	0	0	1 (1.6)
<i>Somnolence</i>	0	1 (2.2)	0	0	1 (1.6)
Gastrointestinal disorders	0	2 (4.3)	1 (16.7)	0	3 (4.7)
<i>Abdominal pain</i>	0	0	1 (16.7)	0	1 (1.6)
<i>Diarrhoea</i>	0	1 (2.2)	0	0	1 (1.6)
<i>Nausea</i>	0	1 (2.2)	0	0	1 (1.6)
General disorders and administration site conditions	0	3 (6.5)	0	0	3 (4.7)
<i>Asthenia</i>	0	2 (4.3)	0	0	2 (3.1)
<i>Feeling hot</i>	0	1 (2.2)	0	0	1 (1.6)
Skin and subcutaneous tissue disorders	0	2 (4.3)	0	0	2 (3.1)
<i>Hyperhidrosis</i>	0	1 (2.2)	0	0	1 (1.6)
<i>Pruritus</i>	0	1 (2.2)	0	0	1 (1.6)

Dx-WBS during ZGrhTSH and L-T₄ withdrawal phases

No distant ¹³¹I uptake lesion revealed by Dx-WBS during ZGrhTSH and L-T₄ withdrawal phases. Among all 64 patients, there were 57 patients (89.1%) showing the concordant scans during the two phases. Of the concordant cases, 8 patients (12.5%) had negative scans, 47 (73.4%) showed thyroidal ¹³¹I uptake, 2 (3.1%) with both thyroidal and extrathyroidal ¹³¹I uptake. Seven patients (10.9%) displayed discordant ¹³¹I uptake, five of which showed positive thyroidal ¹³¹I uptake during ZGrhTSH phase while negative during L-T₄ withdrawal phase, 1 patient had both thyroidal and extrathyroidal ¹³¹I uptake during L-T₄ withdrawal phase, but only thyroidal ¹³¹I uptake presented during ZGrhTSH phase, while the other 1 patient had thyroidal ¹³¹I uptake during L-T₄ withdrawal phase, but negative during ZGrhTSH phase. The

same consistency rate of 89.1% was achieved among the 46 patients in 0.9 mg×2 d group, and the details are presented in Figure 2.

Serum Tg response during ZGrhTSH and L-T₄ withdrawal phases

The mean Tg level was 0.40 ± 0.68 µg/L, and the median was 0.10 (0.10-2.99) µg/L at baseline. After the last dose of ZGrhTSH, Tg rised rapidly to 2.58 ± 5.45 µg/L at 48 hours, with the maximum of 2.61 ± 5.27 µg/L at 72 hours. After a median L-T₄ withdrawal of 23 days, Tg reached to a stable level of 4.81 ± 10.42 µg/L. Serum Tg rised higher after L-T₄ withdrawal than those after last dose of ZGrhTSH ($P<0.001$) (Figs. 3 and 4). By excluding 5 patients with positive TgAb, and using a cut-off Tg level as 1 µg/L, the concordance was 84.7% (50/59), the 100% of concordance were observed in cohorts of 0.9 mg×1d, 1.8 mg×1d, 1.8 mg×2d.

Quality of life during ZGrhTSH and L-T₄ withdrawal phases

No patient experienced hypothyroidism during ZGrhTSH phase while 3 of 49 available cases showed suspicious hypothyroidism during L-T₄ withdrawal phase. The Billewicz Scales score after ZGrhTSH administration was significantly lower than that after L-T₄ withdrawal (-51.30 ± 4.70 vs -39.10 ± 16.61 , $P<0.001$). The specific incidence of hypothyroidism symptoms and signs is shown in Figure 5. The top three symptoms are periorbital puffiness (30/64), weight increase (28/64), and chills (16/64) during L-T₄ withdrawal.

For all patients, the POMS score was 90.10 ± 14.95 at baseline and 91.70 ± 16.70 in ZGrhTSH phase, with the change value of 1.50 ± 12.58 . In L-T₄ withdrawal phase, the POMS score rised to 100.40 ± 22.11 , with the change value of 10.30 ± 21.77 compared with baseline. The POMS score significantly differed between ZGrhTSH and L-T₄ withdrawal phases ($P=0.002$), indicating the mood state of patients after ZGrhTSH administration was significantly better than after L-T₄ withdrawal.

Serum TSH level change during ZGrhTSH and L-T₄ withdrawal phases

The changes of serum TSH had similar trends in all dose groups over time. For all 64 patients, the average level was 0.11 ± 0.12 mU/L at baseline, then reached to the maximum level of 122.11 ± 42.44 mU/L based on 24 hours interval with feasible clinical monitoring sampling time and dropped to near baseline level (0.25 ± 0.28 mU/L) on 14th day after the last dose of ZGrhTSH. During L-T₄ withdrawal phase, serum TSH level reached to the peak (82.20 ± 31.37 mU/L) with a median of 23 days, and maintain stable thereafter, which was significantly lower than that on 24h after last dose of ZGrhTSH ($P<0.001$) (Fig. 6).

Pharmacokinetics of ZGrhTSH

The mean peak TSH concentration for 0.9 mg×1d, 0.9 mg×2d, 1.8 mg×1d, and 1.8 mg×2d groups were 7.49±1.64, 11.94±5.37, 24.09±9.14, 26.42±9.54 ng/mL, respectively, with approximately 12 h for single dose groups and approximately 8-9 h for double doses groups after the last dose of ZGrhTSH (Fig. 7). The half-life of ZGrhTSH clearance from circulation was similar among four regimens with about 20 h after last dose of ZGrhTSH.

Discussion

In this self-control phase I/II clinical study, a rapid rise of serum TSH is observed after ZGrhTSH administration, with a mean peak concentration much higher than that after an average of 23 days of L-T₄ withdrawal, indicating ZGrhTSH could effectively increase serum TSH level instead of the modality of THW. No one developed ZGrhTSH antibodies, suggesting the applicability of multiple ZGrhTSH administration.

The pharmacokinetics of ZGrhTSH were characterized by the durable elevation of TSH levels (>30 mU/L) for at least 72 h after the last dose administration, indicated a relatively slow clearance which is quite similar as it reported in studies of Thyrogen® when comparing with the endogenous TSH [11].

Theoretically, the slow clearance pharmacokinetics feature of rhTSH might be more favorable in aiding the adequate stimulation for RAI uptake and Tg secretion. Of note, serum TSH level could still maintain at about 80% of the peak concentration 24 h after the last dose with an average of 109.1 mU/L and 186.7 mU/L for 0.9 mg and 1.8 mg two days regimen, which allow an adequate TSH stimulation in terms of both duration and high concentration, and also well met clinical routine practice of TSH examination. Though we noticed that the blood concentration of ZGrhTSH increased in a dose-dependent manner, with TSH levels in 1.8 mg groups almost 1-fold higher than that in 0.9 mg groups, the current clinical need for TSH level is indicated as only 30 mU/L and above [12]. One of our prior studies showed that TSH level of 90-120 mU/L was enough in aiding RAI remnant ablation [13]. Hence an average of 100 mU/L for 0.9 mg×2d regimen would be appropriate for both elevation of TSH, and also with a consideration of reducing the potential risk induced by higher TSH level. Thus the 0.9 mg×2d regimen was selected for phase II and subsequent phase III study.

All 64 patients experienced both ZGrhTSH administration and L-T₄ withdrawal for TSH stimulation. Only 13 of the 64 patients suffered ZGrhTSH related AEs, which were generally mild and 11/13 recovered within 1-2 days. The most common AE was headache, with an incidence of 6.3%, and the incidence of other AEs was less than 2%. There was no grade 2 and above ZGrhTSH related AEs, demonstrating the great safety and tolerance of ZGrhTSH. Meanwhile, the Billewicz Scales and POMS score of patients was remarkably higher during L-T₄ withdrawal phase than ZGrhTSH phase, indicating the more hypothyroidism symptoms and dysphoric mood states after THW than ZGrhTSH administration and ZGrhTSH greatly improved the quality of life.

The efficacy of ZGrhTSH has been well demonstrated in terms of promoting RAI uptake and Tg stimulation in this study. A high consistency rate (89.1%) of Dx-WBS findings between ZGrhTSH or L-T₄

withdrawal phases was observed, suggesting ZGrhTSH could effectively enhance sodium-iodide symporter (NIS) expression and corresponding function, thereby improve the iodine uptake. Furthermore, ZGrhTSH seems to be more advantageous in the detection of residual thyroid tissue, with the fact that 5 patients showed positive thyroidal ^{131}I uptake in ZGrhTSH phase while negative in L-T₄ withdrawal phase. Similar phenomenon was also found in Thyrogen® [11]. With regard to stimulate Tg secretion, the modality of L-T₄ withdrawal appears to be more efficient than ZGrhTSH. Serum Tg levels after L-T₄ withdrawal increased almost 2-fold to that after last dose of ZGrhTSH, which is similar to the findings of Thyrogen®. One possible reason might be that continuous TSH stimulation modality could lead to long-standing and more adequate Tg secretion from thyroid follicular cells or DTC cells. Another speculated reason is that the radiation effect of ^{131}I administration at a dose of 3 mCi during ZGrhTSH phase may exert partial ablation effect and cause the damage of follicular cells, which leads to the destructive release of Tg and manifested as higher level in L-T₄ withdrawal phase. The latter could be further evidenced by the mismatch of Dx-WBS finding among patients showed the positive thyroidal ^{131}I uptake during ZGrhTSH phase while negative during L-T₄ withdrawal phase. While the diverse interpretation of such clinical manifestation indicates the need for further exploration and evidence [10, 14].

In conclusion, ZGrhTSH was well tolerated and showed the comparable potential to increase TSH level, improve iodine uptake and stimulate Tg secretion in DTC patients comparing with the L-T₄ withdrawal. Together with the demonstrated better quality of life, ZGrhTSH could be a safe and effective alternative in aiding postoperative evaluation and active surveillance in DTC patients.

Declarations

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Ethics approval

This study was approved by the ethical board of each participated clinical institution. The research was performed with adherence to the guidelines of the Declaration of Helsinki.

Consent to participate

Patients gave informed consent, which included the use of pseudoanonymized data and samples for the purpose of research and publication.

Consent for publication

All authors have read the manuscript and agree with its publication.

Conflict of interest

All authors have no conflicts of interest to disclose.

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Figures

Figure 1

Flow chart of the trial. rhTSH: recombinant human thyroid-stimulating hormone. Dx-WBS: diagnostic 131 I-whole body scan. THW: thyroid hormone withdrawal.

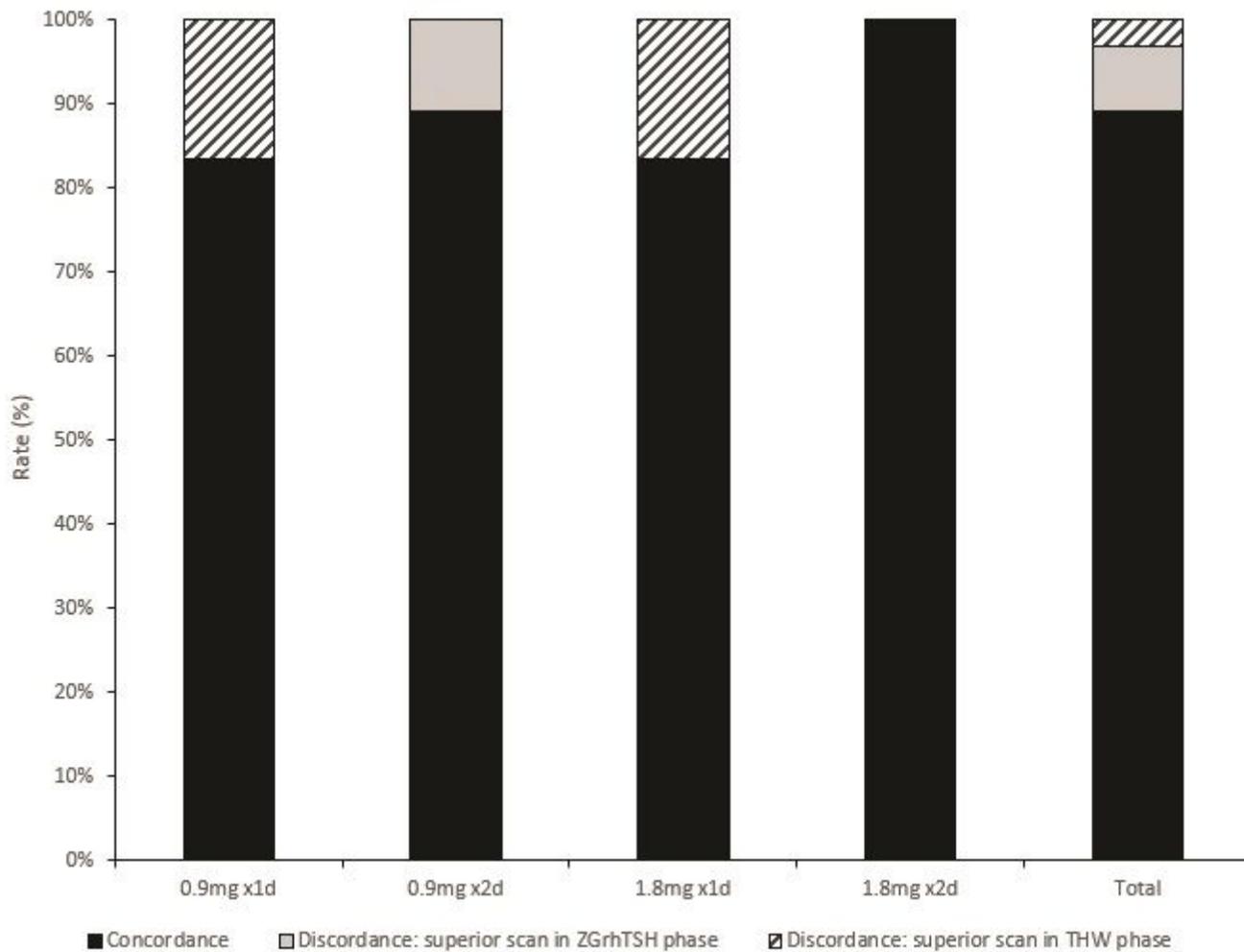


Figure 2

Concordance of Dx-WBS in ZGrhTSH and THW phases. Dx-WBS: diagnostic ¹³¹I-whole body scan. ZGrhTSH: Zelgen recombinant human thyroid-stimulating hormone. THW: thyroid hormone withdrawal.

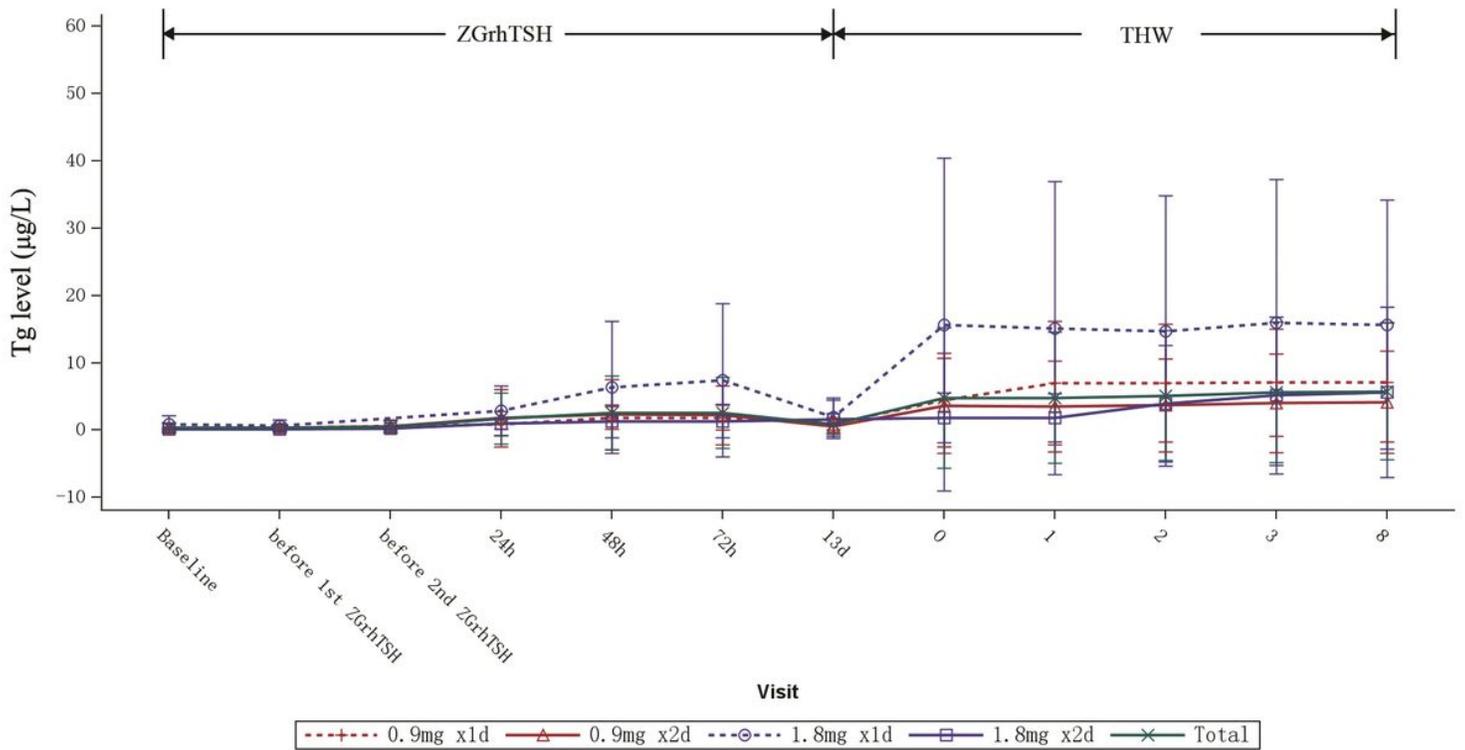


Figure 3

Serum Tg level in ZGrhTSH and THW phases.

0, 1, 3, 8 refer to the day when TSH ≥ 30 mU/L, the next day, the next three days and the next eight days, respectively.

Tg: thyroglobulin. ZGrhTSH: Zelgen recombinant human thyroid-stimulating hormone. THW: thyroid hormone withdrawal.

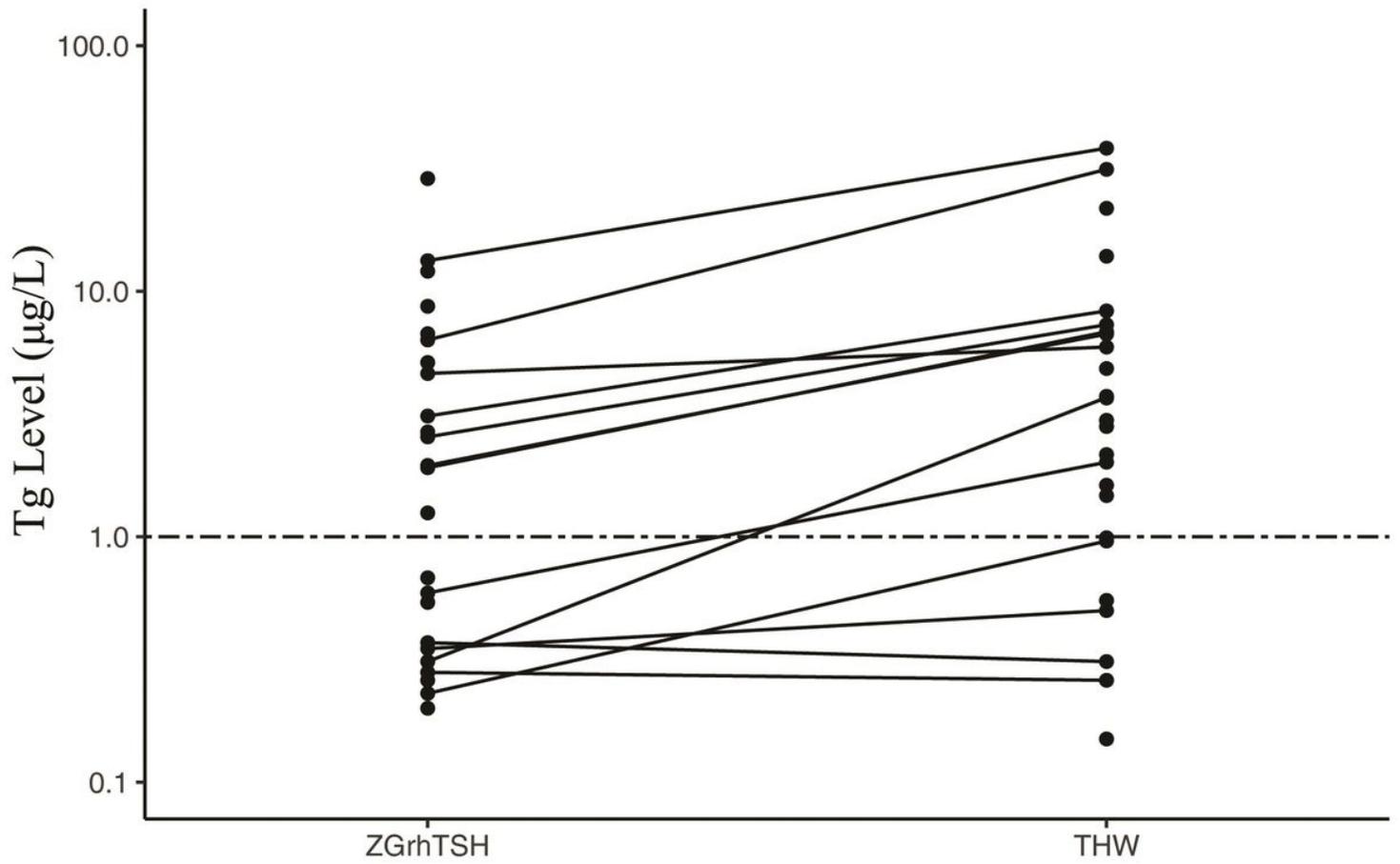


Figure 4

Peak Tg level in ZGrhTSH and THW phases. Tg: thyroglobulin. ZGrhTSH: Zelgen recombinant human thyroid-stimulating hormone. THW: thyroid hormone withdrawal.

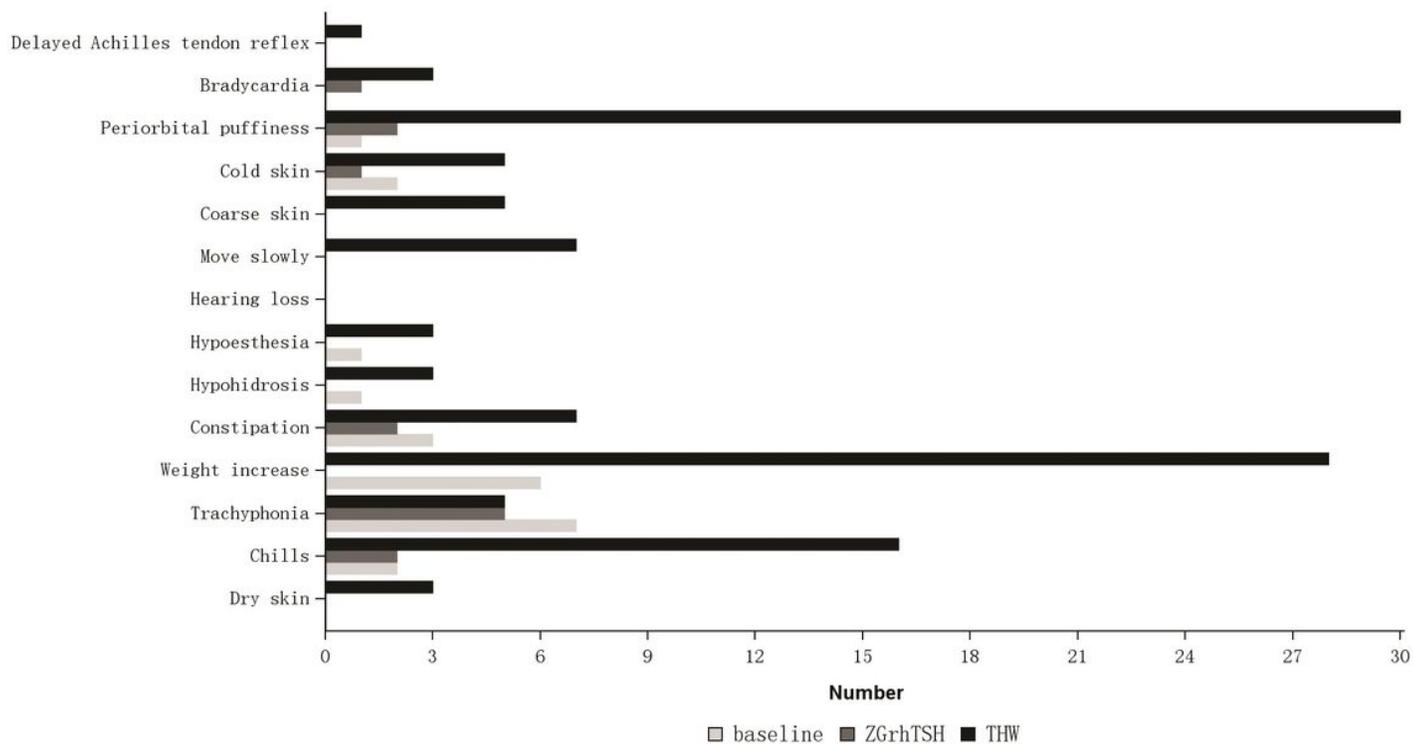


Figure 5

Hypothyroidism symptoms and signs in ZGrhTSH and THW phases. ZGrhTSH: Zelgen recombinant human thyroid-stimulating hormone. THW: thyroid hormone withdrawal.

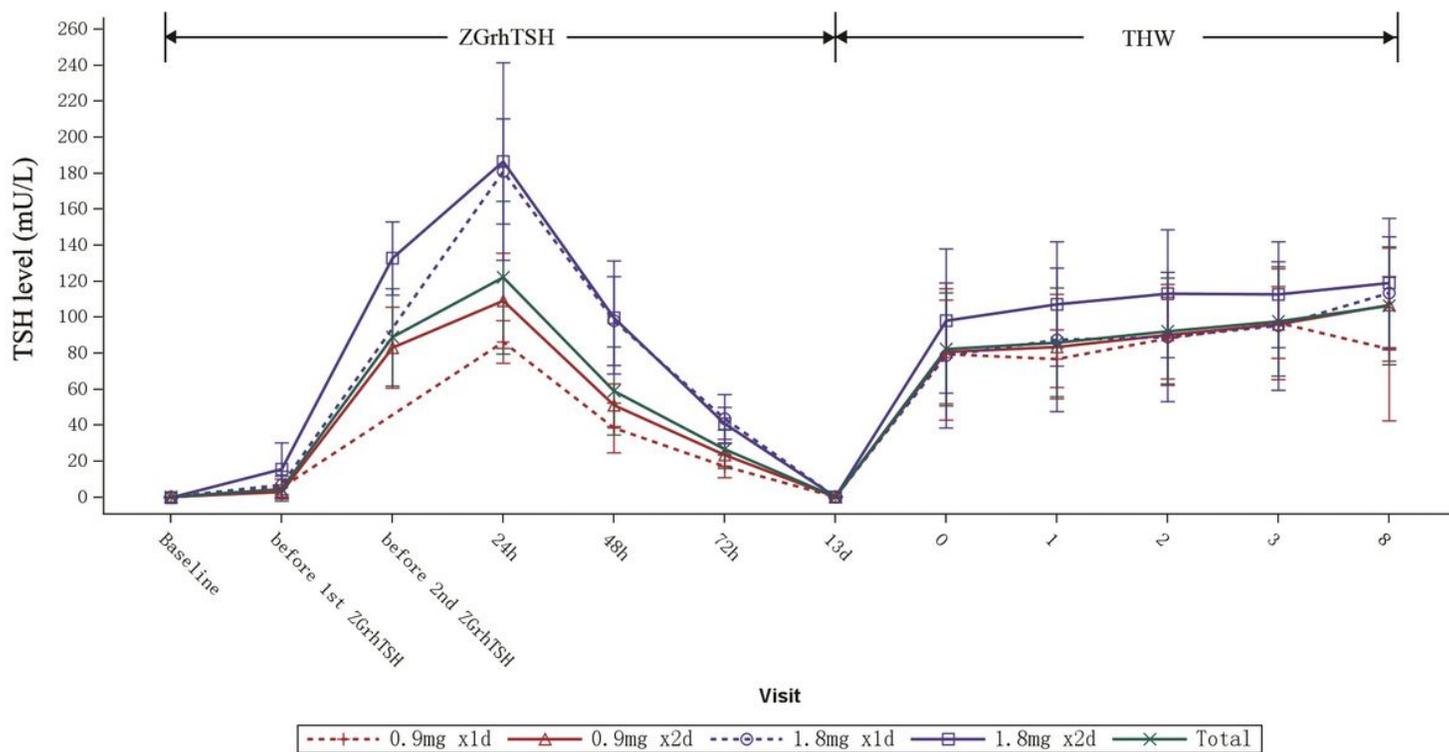


Figure 6

Serum TSH level in ZGrhTSH and THW phases. TSH: thyroid-stimulating hormone. ZGrhTSH: Zelgen recombinant human TSH. THW: thyroid hormone withdrawal.

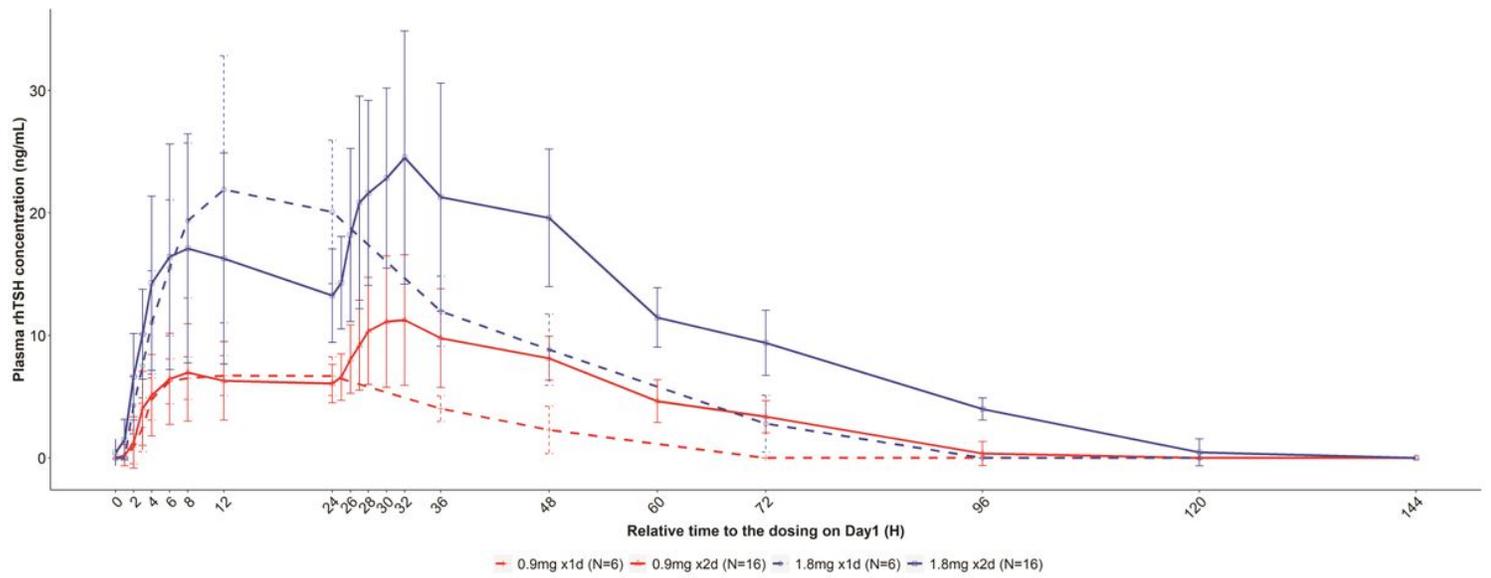


Figure 7

Plasma rhTSH concentration in ZGrhTSH phases. rhTSH: recombinant human thyroid-stimulating hormone. ZGrhTSH: Zelgen rhTSH.