Protocol TSH92-0601: A Study of Safety and Effectiveness of Thyrogen.

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Investigators and Study Center(s)

This was a multicenter study conducted at 5 sites in the United States.

Studied Period

First Patient Enrolled 09 September 1992
Last Patient Completed 08 November 1993

Phase of Development

Phase 3

Objectives

The objective of this study was to determine the safety and effectiveness of Thyrogen® when used as an adjunct in the detection of remnants and metastases in patients with thyroid cancer who have tissue capable of radioiodine uptake.

Methodology

This was a multi-center, open-label, single-arm, well controlled safety and effectiveness study. Prior to study initiation, pre-ablation patients were placed on thyroid hormone suppression therapy (THST) sufficient to suppress thyroid stimulating hormone (TSH) levels to below 0.5 mU/L for a minimum of 4 weeks prior to being treated with Thyrogen®. Post-ablation patients were instructed to either continue their existing THST regimen, if this regimen was successful in suppressing TSH levels, or their THST was adjusted by their physician to suppress TSH levels sufficiently (i.e. <0.5 mU/L). All patients underwent a pre-treatment evaluation, which included a general and thyroid cancer medical history, vital signs, pregnancy test (if applicable), documentation of THST and other concomitant medications, and collection of blood and urine samples. The pre-treatment hypothyroid symptom assessment instruments (Billewicz and profile of mood state [POMS]) were also administered at this time. Patients received a dosing regimen of an IM injection of 0.9 mg of Thyrogen® daily for 2 days while continuing their THST. Twenty-four hours after the final injection of Thyrogen®, vital signs were checked, blood and urine samples were taken, and patients received a scanning dose (2 to 4 mCi) of ^{131}I. Forty-eight hours after ^{131}I administration, patients returned for a whole-body scan (WBS). Prior to this scan, 2 hypothyroid symptoms assessment instruments (Billewicz and POMS) were administered. Following this WBS (Thyrogen® scan), patients continued on THST for at least 2 weeks to allow TSH levels to return to pre-Thyrogen® treatment levels. Patients were withdrawn from this therapy for a minimum of 2 weeks until adequate levels of endogenous TSH ($\geq$25 mU/L) for a WBS were reached.

When adequate TSH levels were reached, vital signs were checked, blood and urine samples were taken, and a measurement of residual radioactivity from the first scan was performed in patients with quantifiable uptake in Thyrogen® scan. Subsequently, the same ^{131}I tracer dose as used for the first scan was then administered and a second WBS (Withdrawal scan) was performed 48 hours later. Prior to this scan, hypothyroid symptom assessment instruments (Billewicz and POMS) were administered. Following the withdrawal scan, the scan results were evaluated and, when indicated, ^{131}I ablation or therapy was performed. One week later, patients returned for follow-up, and a serum sample was taken for immune response testing. Patients were repeatedly queried throughout their participation in the study regarding their THST and concomitant medications and for the presence of any adverse events (AEs).

Number of Patients (Planned and Analyzed)

Number of patients planned was 152; 127 patients were available for efficacy analyses.

Diagnosis and Main Criteria for Inclusion

- Patients with thyroid cancer capable of radioiodine uptake (i.e., well-differentiated thyroid cancer: papillary, follicular, or Hürthle cell).
- Patients who were committed to follow the protocol requirements as evidenced by written, informed consent.
- Patients who were 18 years of age and older.

Test Product, Dose, and Mode of Administration

Thyrogen®, 0.9 mg, was administered daily for 2 days via intramuscular injection.

Duration of Treatment

2 days.

Reference Therapy, Dose and Mode of Administration

Thyrogen®, 0.9 mg, was administered daily for 2 days via intramuscular injection while patients were continuing their THST. Forty-eight hours after ^{131}I, patients returned for a WBS (Thyrogen® scan). After the Thyrogen® scan, patients continued on THST for at least 2 weeks to allow for TSH levels to return to pre-Thyrogen® treatment levels. Patients were withdrawn from this therapy for a minimum of 2 weeks until adequate levels of endogenous TSH ($\geq$25 mU/L) for a WBS were reached.

Subsequently, the same tracer ^{131}I dose used for the Thyrogen® scan was administered, and a second WBS (Withdrawal scan) was performed 48 hours later.

CRITERIA FOR EVALUATION
Efficacy

Evaluation of Radioiodine Scans: Genzyme collected a copy of the images from each WBS for an independent analysis of the uptake e resolution for each image. This review was conducted by 3 independent reviewers who were thyroidology experts, as well as nuclear medicine specialists, and who had not been involved in treating patients in the study. The consensus judgment of 2 or more reviewers for within-patient WBS concordance/discordance and WBS cancer stating was used for efficacy analyses.

Evaluation of Percent Radioiodine Uptake: The percent radioiodine uptake was measured for all foci of thyroid uptake. Percent radioiodine thyroidal uptake was measured by a collimated thyroid probe or region of interest analysis by a digital camera with a computer interface. When it was necessary to discriminate between multiple foci within the neck, measurements were conducted with a pinhole collimator or by region of interest analysis. In certain limited circumstances, dependent on investigational site gamma camera capabilities, a region of interest analysis was used to quantify uptake outside of the neck.

The percent radioiodine uptake measured at the time of the Thyrogen® scan was compared to the uptake measured at the Withdrawal scan. The absolute and percent difference in percent uptake between the Thyrogen® scan and the Withdrawal scan was determined.

Hypothyroid Symptoms Assessment : This assessment consisted of 2 testing instruments, the Billewicz Scale and the short form POMS Scale. The Billewicz Scale is an observer rated scale developed to serve as a diagnostic index for identifying clinical hypothyroidism. Physicians indicate which signs and symptoms of hypothyroidism are present or absent in the patient. The POMS scale is a patient self-administered scale. The POMS scale assesses the areas of tension-anxiety, depression-dejection, anger-hostility, confusion-bewilderment, vigor-activity and fatigue-inertia. The Billewicz and POMS quality of life instruments were administered prior to Thyrogen® administration and prior to each radioiodine scan.

Safety

Vital signs, hematologic signs, blood chemistry, immune response to Thyrogen®, and AEs were evaluated for safety.

STATISTICAL METHODS
Efficacy

Evaluation of Radioiodine Scans in Detection of Remnants and Metastases of Thyroid Cancer: If, based upon the number of pairs of scan for which there was disagreement as to their staging (are not clinically equivalent), the Sign Test was employed at alpha = 0.05 to test the 1-sided null hypothesis that the Thyrogen® scan produces the better staging at least as often as the hormone withdrawal scan. If the numbers of pairs with disagreement in staging did not permit hypothesis testing, a 95% confidence interval (CI) was constructed for the proportion of scans in which the Thyrogen® scan rating was higher than or clinically equivalent to the hormone withdrawal scan rating. The sample size was selected in order that if, as expected, 90% of the pairs were clinically equivalent and the not-clinically-equivalent pairs were evenly divided as to which scan was better, then the CI will imply that the Thyrogen® scan is at least clinically equivalent to the hormone withdrawal scan in 90% of patients.

Comparison of Radioiodine Uptake: The mean absolute and percent difference between the Thyrogen® and hormone withdrawal scans were compared by means of paired t-tests.

Hypothyroid Symptoms: The mean or median change in symptoms from pre-treatment to Thyrogen® scan was compared to that of pre-treatment to hormone withdrawal scan. The analysis of the paired data employed the Wilcoxon Signed Rank test for the Billewicz scale and paired t-tests for the POMS scale and its subscales.

Limitations: Due to the inability to determine the precise disease stage of each patient, disagreements as to the staging as determined by the Thyrogen® and hormone withdrawal scans cannot be resolved. In using the criterion of clinically equivalent or better we presume (in the interest of good clinical practice) that there are no false positives. That is, we assume that any disease noted on either scan is truly present. If this assumption is incorrect, the study findings are correspondingly limited. The study was conducted in nonrandom order with the Thyrogen® scan preceding hormone withdrawal. (Scans presented for evaluation were blinded and in random order). This may have affected (i.e., increased) the sensitivity of the latter (hormone withdrawal) scan. However, this order and its potential bias in favor of hormone withdrawal are unavoidable due to the ethical need to treat immediately any metastases noted on a hormone withdrawal scan. As a result, if the hormone withdrawal were to precede the Thyrogen® scan, only those patients with negative hormone withdrawal scans would be tested with the Thyrogen® scan.

Safety

All safety data were summarized for the safety population. All AEs and serious adverse events (SAEs) were tabulated by body system, preferred term, relationship to study drug, and severity. In the event that AEs were reported more than once, the most extreme level of severity and relationship to treatment was tabulated in the summary tables.

The patient population in this study was 70% female and 30% male, which is consistent with the general patient population for this indication. Patients ranged from 20 to 84 years-of-age, with a mean age of approximately 44.

Efficacy

The results of the scan ratings by the 3 independent reviewers indicate that the Thyrogen® scan was rated equivalent or superior to the Withdrawal scan in 109 of patients in the Per Protocol population. The scan pairs were equivalent in 106 cases and the Thyrogen® scan was superior in 3 cases. In the remaining 18 cases, the Withdrawal scan was rated superior to Thyrogen® scan. When scans were discordant, there was a significant difference in the incidence of superior Withdrawal scans compared to the incidence of superior Thyrogen® scans ($p<0.05$). The results of the Intent-to-Treat (ITT) analysis were consistent with the Per Protocol results. Of the 61 patients with positive scans (evidence of thyroidal uptake), the scan pairs were equivalent in 41 cases and the Thyrogen® scan was superior in 3 cases. In the remaining 17 cases, the Withdrawal scan was rated superior to Thyrogen® scan. When scans were discordant, there was a significant difference in the incidence of superior Withdrawal scans compared to the incidence of superior Thyrogen® scans ($p<0.05$). The result of the ITT analysis was consistent with the Per Protocol analysis result. Of the 22 patients scanned following a recent thyroidectomy and prior to ablation, the Thyrogen® scan was rated equivalent or superior to the Withdrawal scan in 20 of the study patients. The scan pairs were equivalent in 18 cases and the Thyrogen® scan was superior in 2 cases. In the remaining 2 cases, the Withdrawal scan was rated superior to the Thyrogen® scan. The results of the ITT analysis were again consistent with the Per Protocol results. Of the 104 post-ablation patients scanned as part of the monitoring of their disease, the Thyrogen® scan was rated equivalent or superior to the Withdrawal scan in 88 of patients. The scan pairs were equivalent in 87 cases and the Thyrogen® scan was superior in 1 case. In the remaining 16 cases, the Withdrawal scan was rated superior to the Thyrogen® scan. The results of the ITT analysis were consistent with the Per Protocol results.

The rating of each WBS included in the efficacy analyses represents the consensus of at least 2 independent reviewers. Individual reviewers rated the Thyrogen® scan discordant to the Withdrawal scan in 24, 41, and 32 cases, respectively. This difference in individual reviewer rating of study WBSs illustrates the imprecise nature of the WBS technique and the subjective nature of interpreting WBS results.

Disease Staging: In the 62 patients with uptake, 47 patients had uptake limited to the thyroid bed and 15 patients had uptake outside the thyroid bed. Uptake limited to the neck, which was consistent with local metastases, was identified in 9 patients. Uptake consistent with distant metastases was identified in the chest in 4 patients and was elsewhere (e.g., bone or liver) in 2 patients.

Radioiodine Uptake: Quantitative thyroidal radioiodine uptake measurements were performed on all patients to calculate the percentage of activity from the original 2 to 4 mCi scanning dose of ^{131}I (the mean ^{131}I dose administered was 3.22 ± 0.9 mCi), which was sequestered within remnant thyroid tissue, recurrent, or local disease at both the Thyrogen® and Withdrawal WBS (i.e., 48 hours). These measurements were performed with either a thyroid probe or region of interest analysis (ROI) utilizing a digital gamma camera with a computer interface.

Quality of Life: Ninety-four percent of patients had a better quality of life while on Thyrogen® as evidenced by reduced hypothyroid symptomatology using the Billewicz scale. Highly significant differences in quality of life favoring Thyrogen® were found using the short-form Profile of Mood States scale.

Thyroglobulin Response to Thyrogen®: Thyroglobulin (Tg) levels were measured in all study patients 24 hours after the second dose of Thyrogen® (prior to ^{131}I for the Thyrogen® scan) and at the time the patient returned for ^{131}I dosing for the Withdrawal WBS (2 to 4 weeks after THST withdrawal with a TSH level $\geq$ 25 mU/L). These data indicate that post-Thyrogen® Tg levels at 48, 72, or 96 hours are more useful than levels measured 24 hours after Thyrogen® administration.

Thyroglobulin Testing With Thyrogen®: Tg testing with Thyrogen® was evaluated in a cohort of 13 patients who had thyroid cancer confirmed by a WBS that was conducted after the patient received a therapeutic dose of ^{131}I (post therapy scan). All 13 patients had undergone total thyroidectomy, had been ablated, and were Tg-antibody negative. Since these patients had confirmed cancer, it would be expected that the majority would be capable of a Tg response and have sufficiently elevated Tg levels after TSH stimulation to also confirm the presence of cancer. A Tg level of $\geq$ 5 ng/mL was considered a positive result for detecting thyroid cancer in this evaluation. The Tg test that provides the most clinically important information is a Tg test performed after TSH stimulation which identifies cancer that has not been detected by a Tg test while the patient was on THST. Six of the 13 patients in this evaluation had Tg levels <3 ng/mL at enrollment while on THST. Therefore, in these 6 patients, Tg testing during THST produced false negative results. Two of the 6 patients were not capable of a Tg response, as their Tg level remained the same as the level at enrollment even after stimulation with both Thyrogen® and Withdrawal. Tg testing after stimulation with Thyrogen® detected cancer (true positive) in 3 of the remaining 4 patients. Tg testing during Withdrawal detected cancer (true positive) in all 4 patients. The 7 remaining patients had positive results (true positive) at enrollment on THST for thyroid cancer. All 7 patients had an additional Tg response with Tg levels that increased further, both 24 hours after Thyrogen® administration and during Withdrawal.

Safety Results

One patient died due to pulmonary embolism that was considered unrelated to Thyrogen®. One other patient had a serious adverse event of hypotension that was considered related by the treating investigator and the patient recovered. The most commonly reported AEs were nausea in 31 patients, headache in 9 patients, vomiting and asthenia in 5 patients (each), and dizziness in 3 patients.

Patient Immune Response (PIR) to Thyrogen®: The results of testing for a PIR to Thyrogen® indicated that there was no evidence of the development of antibodies specific to Thyrogen® during the study. This includes 7 patients who received a second round of exposure to Thyrogen®.

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