Development and clinical impact of thyroglobulin antibodies in patients with differentiated thyroid carcinoma during the first 3 years after thyroidectomy

R Gögges, M Maniecki, W Jentzen, Sie n-Yi Sheu1, K Mann2, A Bockisch and O E Janssen2

Department of Nuclear Medicine, 1 Institute of Pathology and 2 Division of Endocrinology, Department of Medicine, University of Duisburg-Essen, Hufelandstrasse 55, 45122 Essen, Germany

(Correspondence should be addressed to R Gögges; Email: rainer.goegges@uni-essen.de)

Abstract

Objective and design: Cross-sectional studies have reported an increased prevalence of circulating thyroglobulin autoantibodies (TgAbs) in patients with differentiated thyroid carcinoma (DTC). With the advent of more sensitive assays, a longitudinal study monitoring the development of TgAb levels after ablative therapy was warranted.

Methods: One hundred and twelve consecutive patients with follicular cell-derived thyroid cancer were followed for 3 years. All patients had been thyroidectomized and received, on average, two radioiodine therapies. Residual tissue was quantified scintigraphically by 131I 24-h uptake. TgAb and thyroglobulin (Tg) serum levels were determined with a sensitive direct radioligand assay and an IRMA respectively.

Results: The prevalence of TgAbs at the initial examination was 29% (median 130 U/ml). During follow-up, TgAb levels rose transiently in one-tenth of the patients, but the prevalence of demonstrable TgAbs decreased to 10% after 3 years. The median serum half-life of TgAbs in treated DTC patients was 10 weeks. At initial examination (when all patients still had residual thyroid tissue and 17 had metastases), rising TgAb levels were correlated with the inability to detect Tg in 4, 30 and 73% of the patients, when initial TgAbs were <6, 6–50 or >50 U/ml respectively. While the Tg recovery test was valid for all patients, an in vitro dilution assay with TgAb serum reduced Tg values by up to 32%.

Conclusions: The development and course of TgAbs in DTC patients cannot be predicted by initial or residual tumour volume, TgAb or Tg levels. The presence of TgAbs, even in low concentrations, may cause Tg underestimation despite valid recovery tests in DTC patients.

Introduction

Thyroglobulin (Tg) measurement is the mainstay for the follow-up of patients with differentiated thyroid carcinoma (DTC). As thyroglobulin autoantibodies (TgAbs) are more prevalent in thyroid cancer patients than in the general population (1) and may interfere with Tg determinations, even at low serum levels detected only by sensitive assays (2), the interaction of TgAb with Tg could result in inadequate further diagnostics and treatment of residual or relapsing DTC (3). However, there is no general consensus as to whether the measurement of TgAbs is meaningful for the evaluation of possible interference with Tg measurement, or whether TgAb measurement complements the Tg recovery test (2, 4–6). On the other hand, TgAbs have been proposed as an alternative tumour marker by some authors, but contested by others (7–12). In this prospective study, we report the initial prevalence and course of TgAbs in 112 consecutive DTC patients 3 years after thyroidectomy and radioiodine ablation to evaluate possible interferences with Tg measurement, other confounding factors and their implication for further follow-up. As a model to demonstrate the lowering of Tg values by TgAb, their interference was also evaluated in vitro.

Materials and methods

Patients and clinical procedures

A prospective longitudinal study was performed in 112 consecutive DTC patients (31 males, 81 females; age at the initial examination 17–78 years, median 50 years) who were examined for the first time from June 2000 to August 2001 in our Clinic of Nuclear Medicine and were further treated and regularly followed-up. At each visit, TgAbs were determined unless they had been negative in the last two visits over a maximum time-period of 167 weeks, resulting in a total of 560
serum data samples with three to eight samples per patient. Clinical data available from the further follow-up were included in the evaluation, the entire mean follow-up since initial diagnosis was 33 ± 8 months (mean ± S.D.). The initial examination of the patients took place under thyroid hormone withdrawal in planning the first radioiodine therapy and included a radiiodine scintigraphy of the neck with determination of the 24-h uptake reflecting the amount of remnant thyroid tissue. Prior to ablative radioiodine therapy, thyroid remnants were found in all patients: the $^{131}$I 24-h uptake ranged from 1.0 to 33.5% (median 4.0%). Reports from the historical examination – including possible alterations of the non-tumoral thyroid tissue – were available for all patients. All patients had thyroidectomy and, if necessary, cervical lymph node dissection in either one intervention (25 patients) or two interventions (87 patients). Histology revealed papillary carcinoma in 76 cases, follicular carcinoma in 34 cases and poorly differentiated (insular) carcinoma in two cases. The median time-period between last surgery and initial examination was 23 days. Subsequently, the patients received radioiodine therapy, under endogenous thyrotrophin (TSH) stimulation. Radioiodine therapy was repeated in cases of persistent radioiodine accumulation and detectable Tg at average 4-monthly intervals until no further effect was demonstrated (six patients received one therapy, 86 patients two therapies, 17 patients three therapies and three patients four therapies with activities ranging from 1 to 6 GBq $^{131}$I for the first and from 4 to 10 GBq for further therapies). One year after the final radioiodine therapy, whole body scans were acquired with 0.4 or 1 GBq $^{131}$I.

Apart from the preparation for radioiodine therapies or whole-body diagnostics, the patients were treated with suppressive doses of levothyroxine. After the final radioiodine therapy, patients were followed up at 6-monthly intervals. Work-up included ultrasonography of the neck and measurements of Tg, TgAbs, TSH, free thyroxine and free tri-iodothyronine. Further imaging modalities (X-ray, computed tomography, positron emission tomography) were applied as required.

**Laboratory measurements**

TgAbs were determined with a direct, non-competitive two-step radioligand assay (CentAK anti-Tg; Medipan Diagnostica, Selchow, Germany) calibrated against the international reference preparation NIBSC 65/93 with a factor of two (a TgAb value measured with the CentAK assay is twice as high as the original reference material). The functional sensitivity (referring to the 10% intra- and 20% interassay coefficients of variation) was in the range of 15 U/ml, while the lowest standard of the assay was 6 U/ml. For this study, the analytical sensitivity, similar to the lowest standard in this assay, was used as the lower cut-off. The value of 50 U/ml, which has been established for patients with benign thyroid autoimmune diseases, was used as the upper cut-off level. Tg was measured by an immunoradiometric sandwich assay using two monoclonal antibodies against different epitopes of the molecule (SelCO Tg; Medipan Diagnostica). The functional sensitivity of this assay was 0.5 ng/ml and the lowest standard 0.3 ng/ml. Tg measurements were routinely performed as duplicates and included a recovery test for every sample. Following the manufacturer’s recommendations, patients sera were spiked with 50 ng Tg/ml and recovery calculated as: \[\frac{\text{Tg(patient's serum + recovery buffer)} - \text{Tg(patient's serum)}}{\text{Tg(Tg-free serum + recovery buffer)}} \times 100\%\]. Recoveries between 70 and 130% were considered as valid. Possible in vitro interferences of TgAbs on the Tg measurement were investigated by serum dilution experiments with sera from DTC patients who all had proven metastases. Four different sera with Tg values ranging from 14.0 to 190 ng/ml and negative TgAbs were each diluted 1 + 1 with three sera with extremely high TgAbs (>1000 U/ml) but non-measurable Tg. The diluted sera were incubated for 4 h at room temperature for Tg determinations. Tg values from the mixtures were compared with the values from 1 + 1 dilutions with TgAb- and Tg-negative control serum.

**Statistics**

Statistical differences were evaluated with two-tailed Kruskal–Wallis H test, Mann–Whitney U test or Fisher’s exact test as appropriate. \(P\) values < 0.05 were considered significant. Kinetics of the TgAb decrease were calculated by least square analysis of semilogarithmic plots of remaining TgAb levels vs time.

**Results**

**Patient characteristics at initial examination**

TgAbs at the time of the initial examination (median 23 days after the last surgery) were demonstrable in 32 (29%) of all patients (range 7–1531 U/ml, median 130 U/ml). All these 32 patients had valid recovery tests (89–121%). In 22 of our 112 patients (20%), the initially measured TgAb concentrations even exceeded the value of 50 U/ml (= cut-off for healthy subjects without thyroid disease). Separated by gender, TgAbs were found in two (6%) of all males (19 and 21 U/ml respectively) and in 30 (37%) of all females (range 7–1531 U/ml, median 136 U/ml); the difference in prevalence between men and women was highly significant \((P = 0.001)\) and remained significant even when the different age distribution was taken into consideration. Subgroup analysis of patients with proven metastases \((n = 17\): six males and 11 females, median Tg 13 ng/ml), and those having only thyroid remnants \((n = 95\): 25 males and 70 females, median Tg
1.9 ng/ml) revealed TgAbs only in one case (6%) from the former group, whereas TgAbs were demonstrable in 31 patients (32%) from the latter group. Hence, patients with metastases did not have a higher prevalence of circulating TgAbs than patients who only had thyroid remnants at the first examination. No significant differences were found between both groups concerning $^{131}$I 24-h uptake (median 5 vs 4%) and TSH level (median 40 vs 53 mU/l). To analyze the relationship between measurable Tg values under TSH stimulation and the presence of TgAbs at initial examination, patients were classified into ‘TgAb negative’ (<6 U/ml; n = 80) and ‘TgAb positive’ (>6 U/ml; n = 32). The latter were further subdivided into patients with TgAbs 7–50 U/ml (n = 10) and those with TgAbs >50 U/ml (n = 22). The mean Tg levels as well as the percentage of patients with Tg values above the detection limit were significantly lower in the groups with demonstrable TgAbs, with a further decrease with higher TgAb levels (Table 1). In contrast, the results of the recovery test, the amount of remnant thyroid tissue as reflected by $^{131}$I uptake and the extent of TSH stimulation did not differ significantly between the groups. In order to screen for pre-existing autoimmune thyroid disease (AITD), histology reports from all our patients with initial TgAb values >40 U/ml (n = 23) were re-evaluated. Diffuse lymphocytic infiltration in the non-tumoral thyroid tissue, compatible with Hashimoto’s thyroiditis, was described in ten out of 23 patients. Cases with peritumoral focal lymphocytic infiltrations were excluded, as this is a common finding independent from pre-existing AITD. Together with two more patients in whom Graves’ disease had been established previously, half of the 23 DTC patients had pre-existing AITD. While there is a bias in that these patients were more likely to be evaluated for AITD, at least 11% (12 out of 112) of our DTC patient group had pre-existing AITD. There was no correlation of lymphocytic infiltration with any tumour histology.

**Dynamics of TgAb changes**

The second examination could be performed in 42 outpatients after a relative short time-period (5–14 weeks; median 8 weeks) subsequent to the first radioiodine therapy. At that time, an increase in TgAbs was observed in three (7%) of them (of whom one had been TgAb negative at the first examination, whereas the remaining 28 initially TgAb-negative patients stayed negative). In seven (54%) of the 13 out of 42 patients who had been TgAb positive at the initial examination, TgAbs had already begun to decrease, and in the remaining four TgAb-positive patients the values showed no significant changes. Later, we observed a rise in TgAbs in four additional patients (of whom two had been TgAb negative at the first examination); the respective TgAb peak values were measured 4–8 months after the initial examination. Only one of the overall seven patients with an initial TgAb increase had (disseminated pulmonary) metastases, the remaining six never had active tumour disease during the whole observation period. In the early follow-up period, three patients who were initially TgAb negative became TgAb positive, with no further patients converting later. Including those three initially TgAb-negative patients who converted to positive, 35 of the entire 112 patients (31%) had at least intermittent measurable TgAbs within the initial 3 years following surgery and radioiodine therapy. Subsequent to their respective peak, TgAbs began to decrease continuously in most patients (some times after a latency period of various durations), whereas the finding that values remain measurable at a low level over years was not infrequent. In only two patients (both had papillary carcinoma T2N0M0 without demonstrable tumour disease during the observation period) did the TgAb curve show significant oscillations. The percentage of measurable TgAb values at 6-monthly time-intervals during the observation period is illustrated in Fig. 1. In the time-interval of 1–1.5 years after the first examination, approximately half of the initially TgAb-positive patients became TgAb negative but in nearly one-third of them TgAbs persisted even longer than 3 years after the initial examination (range of the already measurable TgAbs 3–3.5 years after the initial examination: 7–149 U/ml; median 35 U/ml). Figure 2 illustrates the decrease of TgAbs in an individual patient. The median serum half-life after the peak from the

| Table 1 Relationship between circulating TgAbs and measurable Tg values, corresponding TSH and amount of thyroid remnant tissue (reflected by the $^{131}$I 24-h uptake) at the initial examination (prior to radioiodine therapy). |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Group I (TgAbs < 6 U/ml) | Group II (TgAbs > 6 U/ml) | Group IIa (TgAbs 7–50 U/ml) | Group IIb (TgAbs > 50 U/ml) | Significance |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Number of patients               | 80              | 32              | 10              | 22              |                 |
| Percentage of Tg values <0.3 ng/ml | 4%              | 59%             | 30%             | 73%             | a**, b*, c**, d* |
| Tg levels (median of all samples)| 5.0 ng/ml       | <0.3 ng/ml      | 1.3 ng/ml       | <0.3 ng/ml      | a**, b*, c**, d* |
| TSH (median of all samples)      | 47 mU/l         | 57 mU/l         | 48 mU/l         | 59 mU/l         | a, b, c, d = n.s. |
| $^{131}$I 24-h uptake (median)   | 4.0%            | 4.4%            | 3.1             | 4.5%            | a, b, c, d = n.s. |

a = group I vs group II, b = group I vs group IIa, c = group I vs group IIb, d = group IIa vs group IIb; n.s. = not significant; *P < 0.05, **P < 0.001.
fitted curves of the 35 overall patients who had measurable TgAbs values in the course of the observation was calculated as 10 weeks (range 3 – 120 weeks).

**Parameters influencing TgAb dynamics**

Ninety of the total 112 DTC patients were available for follow-up evaluation of TgAb levels after 15 – 18 months after the initial examination (this definite time was chosen for interim results because most patients have finished their radioiodine therapy and have their diagnostic whole body scan between the 15th and 18th months). Of these, 16 (18%) still had positive TgAb levels. These could be divided into one out of seven patients with active tumour disease (percentage of positive TgAbs 17%), six out of 31 patients with thyroid remnants (19%) and nine out of 52 patients without remnant or tumour (17%); thus, the prevalence of TgAbs was similar in these three groups. Furthermore, patients with or without radioiodine accumulating tissue after 15–18 months did not differ significantly with regard to peak TgAb values (median (range) 274 (10–1531) vs 128 U/ml (7–1367)), TgAb half-life (10.5 (4–25) vs 10 weeks (3–120)) and 131I uptake prior to radioiodine therapy (5.4 (1–19) vs 4% (1–13)). Similarly, the presence or absence of TgAbs after 15–18 months in initially TgAb-positive DTC patients was not dependent from 131I uptake prior to radioiodine therapy (3.6 (1–19) vs 4.7% (1–18)). In contrast, the likelihood of negative TgAb testing 15–18 months after the initial examination significantly correlated with the height of initial and peak TgAb values, respectively which had been lower in patients who became TgAb negative after 15–18 months, than in patients with persistent TgAbs (median (range) 66 (7–659) vs 379 U/ml (39–1531), P < 0.01). The only tumour patient with persistent TgAbs also had a high initial TgAb value (715 U/ml). Peak TgAb values and TgAb values of the DTC patients 15–18 months after the initial examination were positively correlated (Pearsons’ r = 0.673; P < 0.001).

**TgAbs did not influence the progression of the disease**

After 3 years of follow-up, 103 of the 112 patients (92%) had complete or partial remission. Of the remaining patients, one had stable disease (persisting disseminated pulmonary metastases after three high-dose radioiodine therapies), five had progressive disease resulting in two tumour-related deaths and three had recurrent disease. Neither the initial TgAb levels, nor the presence of circulating TgAbs at the 15–18 month evaluation, nor the TgAb half-life were correlated with the course of the disease. As expected, all three recurrences were accompanied by rising Tg levels. Only one of the 17 patients with active tumour disease had demonstrable TgAbs (TgAbs initially 715, peak level 881 U/ml). This patient with moderately well differentiated papillary carcinoma (T4 N1 M1) was the only patient with incongruent low Tg levels (maximum 0.7 ng/ml under TSH stimulation) despite an extensive tumour mass (persistent radioiodine-accumulating bipulmonary metastases).

**Interference of TgAbs with Tg determination in vitro**

To examine in vitro interference of TgAbs with Tg measurements, dilution experiments were performed. All samples were obtained from DTC patients with proven metastases. Four Tg test sera with undetectable TgAbs were each diluted 1 + 1 with one Tg- and TgAb-free control serum and three Tg-negative sera with TgAb levels >1000 U/ml. In comparison with
the control serum, dilution with TgAb-positive sera reduced the Tg values by as much as 32% (Table 2). Tg recoveries tended to be lower when diluted with TgAb-positive samples but remained in the range considered as undisturbed (70–130%).

Discussion

Prevalence and development of TgAbs in DTC patients

Previous studies have reported a higher prevalence of TgAbs in DTC patients than in the general population. Using a highly sensitive radioligand assay and a lower cut-off level, Spencer et al. (2) found a higher percentage of circulating TgAbs (25% of 213 DTC patients) as described in previous studies. Since only a few longitudinal studies on TgAb development which used less sensitive assays have been published (1, 7) and the more recent studies which used newer, more sensitive assays (2, 13) only analyzed TgAb and a Tg in cross-sectional data, we now present a longitudinal study using a sensitive direct radioligand assay for TgAb and an IRMA for Tg to correlate their development with residual tumour tissue and with therapeutic interventions. Several recent systematic histopathological studies have reported a higher prevalence of coexisting lymphocytic thyroiditis (14–16) or Graves' disease (17) in DTC patients before surgery compared with controls. In contrast, Rubello et al. (18) reported preoperative elevated TgAb levels > 50 U/ml in 43 (11.2%) of 384 DTC patients, of which only five (1.3%) had coexisting autoimmune thyroiditis. It has not been proven whether TgAbs deriving from benign AITD also recognize epitopes on tumoral Tg from the respective patient and/or may cause interference with Tg measurement during oncologic follow-up. The TgAb kinetics in the course of patients with proven pre-existing lymphocytic thyroiditis did not differ significantly from that of patients without pre-existing AITD when evaluating only those cases in whom the initial TgAbs where higher than 40 U/ml. Quevedo et al. (11) measured TgAb values in the course of the first 3 years in 26 DTC patients of whom 19 had coexisting lymphocytic thyroiditis and found significantly higher TgAb values in these patients as compared with those without thyroiditis. Chiovato et al. (19) measured TgAbs using passive agglutination kits in the course of observation of 116 patients with DTC who initially had positive results for these antibodies, and of whom ten patients had coexisting Graves' disease and 34 patients Hashimoto's thyroiditis. The mean time of disappearance of TgAbs was 3 years and thus somewhat longer than in our study. Since in most patients the disappearance of TgAbs was associated with the disappearance of thyroid tissue, this difference may be due to a different ablative concept in radioiodine therapy; in nearly two-thirds of their patients thyroid tissue was still demonstrable 15–18 months after the initial examination, while this was only the case in 48% of the patients in our study. Similar to our results, Chiovato et al. (19) found no significant differences in the pattern of disappearance of TgAbs in patients with coexisting Hashimoto's thyroiditis or Graves' disease and in patients with focal auto-immune thyroiditis. Although we observed the tendency that patients with a higher peak TgAb value had a higher probability of still measurable TgAb values at the end of the observation period, the course of TgAbs in the individual patient displayed a large variability and cannot be predicted by one of the investigated parameters alone (initial TgAb value, initial amount of thyroid remnant tissue, coexisting AITD, initial prevalence of tumour tissue, persistence of scintigraphically demonstrable thyroid remnant or of tumour tissue at the time-interval 15–18 months after the initial examination). The use of TgAbs as a prognostic parameter in DTC remains controversial. While Rubello et al. (18) and Adil et al. (12) reported a higher frequency of relapse in association with persisting TgAbs after ablative therapy, the majority of authors (1, 8, 10, 11) found no correlation, in agreement with our data.

<table>
<thead>
<tr>
<th>Test sera (TgAb and Tg negative)</th>
<th>Control serum (TgAb and Tg negative)</th>
<th>Sample no. I</th>
<th>Sample no. II</th>
<th>Sample no. III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tg (ng/ml)</td>
<td>Recovery (%)</td>
<td>Tg (ng/ml)</td>
<td>Deviation (%)</td>
</tr>
<tr>
<td>Sample no. 1</td>
<td>6.3</td>
<td>102</td>
<td>6.4</td>
<td>0</td>
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<tr>
<td>Sample no. 2</td>
<td>30.3</td>
<td>98</td>
<td>28.4</td>
<td>−3</td>
</tr>
<tr>
<td>Sample no. 3</td>
<td>44.7</td>
<td>98</td>
<td>37.1</td>
<td>−17</td>
</tr>
<tr>
<td>Sample no. 4</td>
<td>94.9</td>
<td>95</td>
<td>90.5</td>
<td>−5</td>
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</table>
Interference of TgAbs with Tg measurement in DTC patients

The new commercial Tg immunoradiometric assay (IMA) have a lower detection limit far below 0.5 ng/ml with a satisfactory intra- and interassay precision (20–22). However, several problematic aspects impeding the correct measurement and interpretation remain (23, 24). It is still controversial as to whether circulating TgAbs prevent reliable Tg measurement even when a recovery test is undisturbed. TgAb interference can produce either under- or overestimation of serum Tg. While Tg IMAs typically underestimate serum Tg when sera contain TgAbs, presumably because the endogenous Tg complexed with TgAbs cannot interact with the assay antibodies, RIAs can under- or overestimate Tg depending on the assay antibodies (2, 4). In contrast, Mariotti et al. (25) postulated that the low Tg values observed in some patients who also have TgAbs could be due to an accelerated metabolic clearance rate of the Tg–TgAb complexes.

On the other hand, circulating TgAbs – even in high serum concentrations – do not necessarily interfere with the Tg measurement (2), and reasons other than TgAb interference may cause unreliable Tg values. Finally, not only Tg but also TgAb assays can produce unreliable results, e.g. because of interfering high Tg concentrations (26) or epitope incompatibility between TgAbs and the radioligand (Tg) on the one hand and radioligand and assay antibodies on the other hand (27). Thus, the determination of TgAbs may not always be the ideal tool to authenticate Tg measurements. To solve this problem, Tg recovery tests have been introduced, allowing for a control as to whether a defined amount of Tg added to the patients’ serum sample is measured adequately. However, the usefulness of recovery tests and their value for recognizing Tg–TgAb interferences have been disputed. Some authors (2, 4) stress that recovery tests cannot be used to validate a Tg measurement in serum containing TgAbs. In particular, they have postulated that the epitopes on the exogenous Tg molecules (glandular origin) may differ from the epitopes of endogenous, tumorous Tg in the patients’ serum. In contrast, others have emphasized the importance of recovery tests instead of TgAb measurements (5, 6).

Finally, some authors recommend the performance of recovery tests and TgAb measurements in parallel (13) to recognize all kinds of interference, including a possible high-dose-hook effect. We observed a significant proportion of patients with unexpectedly low or negative Tg values despite proven thyroid remnants or metastases. Their sera were more often TgAb positive or had higher levels of TgAbs than sera with Tg values above the detection limit. This was not merely a problem of the routine IRMA but was verified with a sensitive immunoluminometric assay using different antibodies. Thus, we found a correlation of low measurable Tg values and circulating TgAbs. The decrease in Tg values in the dilution experiments was also compatible with an in vitro interference of Tg and TgAbs in Tg IMAs despite an undisturbed recovery. However, the clinical implication is very limited, as only one patient had negative Tg associated with positive TgAb at some determinations, although she had metastatic DTC. She would have been picked up anyway because of a suggestive radiiodine scan.

In conclusion, our data add a note of caution to the interpretation of low or negative Tg values measured by IMA methods in the presence of circulating TgAbs as they might be caused by in vitro interference. In agreement with the guidelines for in vitro and in vivo procedures for thyroid diseases of the German Society of Nuclear Medicine (3) we recommend a screening test for TgAbs at the initial Tg measurement and further controls in cases of elevated TgAb values. We further recommend measurement of both Tg and TgAbs in all patients with higher risk profiles (e.g. tumour stage T4 or N1/M1, special histologic subtypes with poor prognosis or recurrent disease) with low or negative Tg values, even when previous TgAb measurements had been negative, employing sensitive direct assays and also taking into account measurable TgAbs values below the usual cut-off established forAITD. Normal recovery tests do not exclude false negative Tg values due to TgAb interference. However, they are essential to discover a high-dose-hook effect and other reasons for disturbed Tg measurements which are not recognized if only TgAb measurements are performed. Some of these problems may also be solved by simply using lower Tg amounts in a ‘low-dose’ recovery test as suggested by Morgenthaler et al. (20) and others. We hypothesize that a modified architecture of the recovery test regarding the origin and amount of added Tg may overcome most of the current problems of epitope variability and affinity.

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