Rosiglitazone Effect on Radioiodine Uptake in Thyroid Carcinoma Patients with High Thyroglobulin but Negative Total Body Scan: A Correlation with the Expression of Peroxisome Proliferator–Activated Receptor-Gamma

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Background: Thyroid carcinoma patients with high thyroglobulin (Tg) level but negative total body scan (TBS) are difficult to treat with radioiodine (RAI). The objective of this study was to determine if treatment with rosiglitazone (RZ), a peroxisome proliferator–activated receptor-gamma (PPAR-γ) agonist, was associated with an increase in RAI uptake in thyroid carcinoma patients with high serum Tg and negative TBSs. We also determined if there was a correspondence between the effect of RZ and the degree of staining for PPAR-γ within thyroid cancer tissues.

Methods: We prescribed 8 mg of RZ daily for 6 weeks in 23 patients with epithelial cell thyroid carcinoma who previously had negative posttherapeutic I-131 total body scans (post Rx TBSs) with high serum Tg concentrations. Diagnostic total body scans (Dx TBSs) before and 6 weeks after RZ treatment were compared. An ablative dose of I-131 was then given to all patients, and post Rx TBS was performed to evaluate RAI uptake. Immunohistochemical staining of PPAR-γ expression in thyroid cancer biopsies was done to correlate this with possible effects of RZ on RAI uptake.

Results: Seven patients had strong PPAR-γ–positive staining in thyroid biopsies, nine patients had weakly positive staining, and seven patients had negative staining. Five of seven patients with strong staining had either positive post Rx TBS, or both Dx TBS and post Rx TBS. One of nine patients with weak staining had positive Dx TBS and post Rx TBS. In contrast, none of the seven patients with negative staining had positive TBS.

Conclusions: RZ can increase RAI uptake in thyroid tissue in the majority of patients with epithelial cell thyroid carcinoma whose previous posttherapeutic I-131 scans were negative provided they have high intensity and extent of PPAR-γ expression in thyroid tissue. Few, if any, patients with weak or no PPAR-γ expression in thyroid cancer tissue increase RAI uptake after RZ treatment.

Introduction

Epithelial cell thyroid cancer is the most common endocrine cancer. Papillary and follicular thyroid carcinomas are referred to as well-differentiated thyroid cancer. They account for 80–90% of all thyroid cancers (1). If detected early, most papillary and follicular thyroid cancers can be successfully treated by a total or a near-total thyroidectomy followed by administration of radioiodine (RAI). RAI therapy remains the cornerstone of management for metastatic thyroid cancer. When administered under optimal conditions, it can achieve either eradication or long-term clinical control of the disease (2). Papillary and follicular thyroid carcinomas can later transform (dedifferentiate) into less-differentiated forms (3–7). These are more aggressive and difficult to treat with RAI due to nonavid uptake (8). Variants of thyroid cancer, such as tall cell, solid/trabecular, columnar, and the less-differentiated forms, are more likely to have nonavid RAI uptake. Tumors that do not concentrate RAI may require chemotherapy, but the results of this are poor and associated with toxicity. Various attempts have been made to augment RAI therapy but the benefits have been marginal. Preclinical and clinical studies of agents that induce redifferentiation (9), growth inhibition (10),...

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promotion of apoptosis, and cell cycle regulation have been reported (11) with varying success. Among these promising agents is a group of drugs used for treatment of type II diabetes mellitus, the thiazolidinediones (TZDs). Drugs in this class that are available in Thailand include rosiglitazone (RZ) (Avandia®) and pioglitazone (Actos®). These agents act as a peroxisome proliferator–activated receptor-gamma (PPAR-γ) agonists. Nuclear hormone receptors, such as PPAR-γ and retinoid X receptor, are variably expressed in thyroid carcinoma cell lines. Expression of these receptors may predict thyroid cancer cell response to treatment with retinoids and TZDs (11). PPAR-γ is involved in a wide range of cellular processes (12). Other than the known action on insulin sensitization, adipocyte differentiation, and lipid storage (13–15), it also has an effect on the cell cycle, inflammation, atherosclerosis, apoptosis, and carcinogenesis (12). It has been observed that PPAR-γ is expressed more in thyroid carcinoma areas than in adjacent normal thyroid tissue (16). Although receptor expression is necessary for inhibition of thyroid carcinoma growth, it may or may not be sufficient for treatment response. Although a good response could be observed in a trial using troglitazone for the treatment of prostate cancer (17), a controlled trial showed that RZ neither increased the doubling time of prostate-specific antigen nor prolonged the time to the disease progression (18). There have been only a few preliminary clinical trials that used TZDs for treatment of thyroid carcinoma. Therefore, we studied the effect of RZ on reuptake of RAI and thyroglobulin (Tg) expression in patients with non-RAI-avid, high Tg thyroid carcinoma.

Materials and Methods

Patients

Thyroid carcinoma patients included in this study had high levels of serum Tg (>10 ng/mL) and met the following criteria: (i) a history of previous RAI avidity on diagnostic total body scan (Dx TBS) but later no RAI uptake on recent Dx TBS and 1-week posttherapeutic (5550 MBq of I-131) total body scan (post Rx TBS) within 6-month period prior to enrollment; (ii) available tissue for PPAR-γ-specific immunohistochemical staining; (iii) more than 18 years old; and (iv) a Karnovsky score of more than 70%. Pregnant or nursing mothers were excluded. Also excluded were patients with diabetes mellitus type I, a history of previous treatment with TZDs, poor liver function (serum alanine aminotransferase [ALT] more than 2.5 times of the upper limit), anemia, a tendency to develop congestive heart failure, and positive serum anti-Tg antibodies.

The study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. The diagram of the study is shown in Figure 1. Procedures and potential side effects of the drug were explained, and informed consent was obtained from subjects. Age, sex, Karnofsky score, evidence of tumor by other imaging modalities (if present), tissue cell types, PPAR-γ staining results, Tg levels, and the results of TBS were recorded. Blood tests for liver function (aspartate aminotransferase [AST], ALT, and total and direct bilirubin), fasting plasma glucose levels, and hemoglobin concentration were obtained before and immediately after stopping RZ treatment to assess side effects. RZ was administered orally at the dose of 8 mg daily for 6 weeks. The Dx TBS was performed before (Dx TBS1) and within 1 week after stopping RZ treatment (Dx TBS2) to assess the effect of RZ on RAI uptake. For the Dx TBS, 74 MBq of RAI was given orally when the serum thyrotropin (TSH) level was higher than 30 mIU/L. To achieve a high serum TSH, patients were prepared by decreasing the daily L-thyroxine to ¼ of the usual dose for 4 weeks and then withdrawing L-thyroxine for 2 weeks. External sources of stable iodine were strictly controlled for 6 weeks before each Dx TBS as it is the usual protocol in our center. After the first Dx TBS, the usual dose of L-thyroxine was resumed for 1 month to normalize the serum TSH before Dx TBS2. The anterior and posterior views of Dx TBS were taken using the dual-headed gamma camera (Trionix-Blad, Twinsburg, OH) equipped with high-energy collimator at 48 hours after RAI administration. The matrix size was 512×1024, and the detector speed was at 10 cm/min. The Dx TBS1 and Dx TBS2 were compared. High dose (5550 MBq) of RAI was given irrespectively of the Dx TBS2 result. Both the dose for Dx TBS and the dose for RAI therapy were equal to the preenrollment doses in order to minimize the difference between scans. One-week after 5550 MBq RAI therapy, post Rx TBS was again assessed and compared to the last post Rx TBS. All scans were assessed without knowledge of the PPAR-γ staining results. The uptake of RAI in each study was scored as follows: 0 = no abnormal uptake (uptake at the suspected tumor site is equal to body background at the left shoulder); 1 = faint uptake (ratio of tumor uptake to background at the left shoulder > 1.5 but lesser than 2); 2 = good uptake (ratio of tumor uptake to background at the left shoulder > 2). Levels of Tg, anti-Tg, and TSH were also assessed. Comparison of the data was made for the Dx TBS1, Dx TBS2, and Dx TBS at 6 months after RAI treatment.

Immunohistochemistry

PPAR-γ protein expression was determined by immunohistochemical staining of thyroid cancer tissues. Serial sections (3 μm) of paraffin-embedded tissue were processed for PPAR-γ-specific staining. Tissue sections were deparaffinized. Endogenous peroxidase was quenched by preincubating the tissues with 3% hydrogen peroxide for 5 minutes. The tissues were then washed with phosphate-buffered saline (PBS). Staining with monoclonal mouse antihuman PPAR-γ antibody (Santa Cruz Biotechnology, Santa Cruz, CA) used at 1:100 dilution was then performed at room temperature for 60 minutes. The tissue was washed again with PBS. After sections were stained with unique enzyme-conjugated polymer backbone, which also carries secondary antibody molecules, the immunoreactivity was visualized by incubating the slides with diaminobenzidine. The slides were then washed, counterstained with hematoxylin, dehydrated with alcohol and xylene, and mounted with a permanent mounting medium. Adipose tissue was used as a positive control. For a negative control, no primary anti-PPAR-γ antibody was added. A pathologist who did not know the patients’ information examined the stained slides and scored the levels of nuclear staining as negative stain, weak stain, or strong stain as shown in Figure 2, respectively. The percentage of PPAR-γ–positive staining area to the whole tumor area was also assessed in strong PPAR-γ–positive tissues.
Analysis

To evaluate effect of RZ on RAI uptake, the change of RAI uptake score in the tissue from Dx TBS1 to Dx TBS2 and to post Rx TBS was assessed. Good response to RZ was defined as an increase in scores of Dx TBS2 as compared to that of Dx TBS1, or an increase in the score of post Rx TBS as compared to that of Dx TBS1. No response to RZ was defined, as there was no change in the uptake score.

For effect of RZ on tumor growth, Tg levels between Dx TBS1 and Dx TBS2, Dx TBS1 and Dx TBS at 6 months post-RAI treatment were compared using paired t-test. A decreased level of Tg represented good response, while unchanged or increased Tg levels represented no response or more rapid tumor growth than the effect of tumor resection. Comparison of Tg change from Dx TBS1 to Dx TBS2 and from Dx TBS1 to Dx TBS at 6-month follow-up was performed between each groups of PPAR-γ expression using unpaired t-test. The levels of TSH during Dx TBS1, Dx TBS2, and Dx TBS at 6-month follow-up were compared using paired t-test. Statistical significance was set at p < 0.05.

Results

Serum AST, ALT, total and direct bilirubin, fasting plasma glucose, and hemoglobin were similar after stopping RZ treatment compared to baseline. Of the 101 patients who had high serum Tg concentrations and underwent 5550 MBq RAI therapy, there were 39 patients with both negative Dx TBS and post Rx TBS who met this criteria for the study. All these patients had negative serum anti-Tg antibody tests. Sixteen of the 39 patients were excluded because there was no tissue available for PPAR-γ-specific staining. Table 1 presents the biographical data, cell type, PPAR-γ-specific staining, and TBS of the 23 patients who met all of the study criteria. Tissues for PPAR-γ-specific staining were obtained from recurrent tumor tissue in six of the seven patients who had strong PPAR-γ expression, five of the nine patients who had weak PPAR-γ expression, and two of seven patients who had negative PPAR-γ expression. In those patients whose tissues for PPAR-γ-specific staining were not obtained from recurrent tumor tissue by biopsy at the time of recurrence, the tissues were obtained from either thyroid tissue or cervical lymph node metastases from the first surgery.
Of the 23 patients, 7 had strong PPAR-γ–positive staining, 9 had weakly positive staining, and the remaining 7 had negative staining. The majority of the strong PPAR-γ–positive patients had papillary cell type with less differentiation. All, but one (patient J.K.), strongly positive patients had more than 80% of the examined area positive for PPAR-γ staining. Five of seven patients with strong PPAR-γ–positive staining showed either positive post Rx TBS alone or both Dx TBS2 and post Rx TBS. In contrast, only one patient with weakly positive staining had positive TBS. No patients with negative stain had positive TBS (Table 1). Examples of positive effect of 6-week treatment of RZ on Dx TBS2 and post I-131 Rx TBS are shown in Figure 3.

Serum Tg concentrations at the time of Dx TBS1 (pre-RZ), Dx TBS2 (post-RZ), and at 6 months after RAI and RZ treatment (for 6 weeks) (post–RZ + I-131) along with PPAR-γ staining information are shown in Figure 4. Serum TSH concentrations were similar in the groups classified according to PPAR-γ staining at all times. Changes in serum Tg levels at the various time points of the study were similar among the groups based on PPAR-γ staining classification. Serum Tg concentrations were similar at the time of Dx TBS1 and Dx TBS2, and at the time of Dx TBS1 and Dx TBS at 6-month follow-up. There were two patients (P.R. and J.L.) with strong PPAR-γ staining and positive post Rx TBS; however, they showed substantial declines in serum Tg level after RZ administration and a steep decline in serum Tg 6 months after I-131 treatment (from 5611 to 5592 ng/mL and to 2755 ng/mL in one patient, and from 202 to 195 ng/mL and to 7 ng/mL in another patient). In contrast, there was no substantial decline in serum Tg in any patient in the weak or negative PPAR-γ staining group (Fig. 4). The last points in Figure 4 are missing due to rapid tumor growth that led to changes in treatment before the 6-month follow-up Dx TBS with serum Tg could be performed.

Discussion

Our study showed a trend toward positive effects of RZ in patients with strong PPAR-γ receptor–positive staining in increasing RAI uptake in thyroid carcinoma patients with previously negative TBS. The majority of the patients (five of seven) with strong PPAR-γ–positive staining and one of nine patients with weakly positive staining had RAI uptake post Rx TBS plus RZ, even though some had negative Dx TBS. The reason for the negative Dx TBS may be the reported low sensitivity of Dx TBS compared with post Rx TBS (19–22). Thus, administering additional 5550 MBq I-131 was designed to detect more positive lesions and also to give a chance for the therapy in whom the post Rx TBS was positive. The positivity of post Rx TBS in this study is likely due to the RZ effect, not of the effect of the higher dose of post Rx TBS than Dx TBS, because all patients had a history of negative last post Rx TBS before enrollment.

What is the underlying mechanism of different responses to RZ? There was a previous study in papillary cell lines that demonstrated that for a cellular response to TZDs, PPAR-γ expression is necessary (11). Therefore, the effect of TZDs is driven by a receptor, not by a drug effect via a secondary pathway. This supports our study showing that patients with strong PPAR-γ expression tend to demonstrate more RAI uptake after RZ administration than those with weak or negative PPAR-γ expression. We observed that in strong PPAR-γ–positive patients, the responses were inhomogeneous among different cell variances. Patients with columnar cell and tall cell variants of papillary carcinoma,

FIG. 2. Peroxisome proliferator–activated receptor-gamma (PPAR-γ) staining levels in thyroid cancer patients. (A) H&E (×400), (B) negative, (C) weakly positive, (D) strongly positive PPAR-γ immunohistochemical staining; magnification: ×400.
### Table 1. Biographical Data, Cell Type, PPAR-γ Expression, Dx TBS after 6 Weeks of RZ, and 6 Weeks of RZ Plus 5550 MBq I-131 Rx TBS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Cell type</th>
<th>Tissue obtained from</th>
<th>PPAR-γ expression intensity/area stain</th>
<th>Dx TBS after RZ/site (score)</th>
<th>Post Rx TBS/site (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.R.</td>
<td>49</td>
<td>F</td>
<td>Papillary, columnar cell variant</td>
<td>Neck, recurrent</td>
<td>Strong/80%</td>
<td>–ve</td>
<td>+ve/neck (1) and lung (2)</td>
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<tr>
<td>S.L.</td>
<td>40</td>
<td>F</td>
<td>Follicular</td>
<td>Neck, recurrent</td>
<td>Strong/90%</td>
<td>+ve/bone (1)</td>
<td>+ve/bone (2)</td>
</tr>
<tr>
<td>J.L.</td>
<td>56</td>
<td>F</td>
<td>Papillary, tall cell variant</td>
<td>Neck, recurrent</td>
<td>Strong/90%</td>
<td>+ve/neck (1)</td>
<td>+ve/neck (2)</td>
</tr>
<tr>
<td>J.K.</td>
<td>57</td>
<td>M</td>
<td>Papillary</td>
<td>Neck, recurrent</td>
<td>Strong/10%</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>S.P.M.</td>
<td>81</td>
<td>F</td>
<td>Papillary, tall cell variant</td>
<td>Trachea, recurrent</td>
<td>Strong/90%</td>
<td>+ve/neck (1)</td>
<td>+ve/neck (2)</td>
</tr>
<tr>
<td>N.G.K.</td>
<td>67</td>
<td>F</td>
<td>Papillary, solid/trabecular variant</td>
<td>Neck, recurrent</td>
<td>Strong/90%</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>N.S.C.</td>
<td>32</td>
<td>M</td>
<td>Mixed papillary–follicular</td>
<td>Neck node, original</td>
<td>Strong/80%</td>
<td>–ve</td>
<td>+ve/lung (1)</td>
</tr>
<tr>
<td>A.S.</td>
<td>59</td>
<td>F</td>
<td>Papillary</td>
<td>Neck, recurrent</td>
<td>Weak</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>L.T.</td>
<td>61</td>
<td>F</td>
<td>Papillary, tall cell variant</td>
<td>Neck, recurrent</td>
<td>Weak</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>N.S.</td>
<td>72</td>
<td>F</td>
<td>Papillary, tall cell variant</td>
<td>Thyroid, original</td>
<td>Weak</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>S.P.S.</td>
<td>72</td>
<td>M</td>
<td>Papillary</td>
<td>Neck, recurrent</td>
<td>Weak</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>S.T.</td>
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<td>F</td>
<td>Papillary</td>
<td>Thyroid, original</td>
<td>Weak</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>U.C.</td>
<td>66</td>
<td>F</td>
<td>Papillary</td>
<td>Neck, recurrent</td>
<td>Weak</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>K.P.</td>
<td>44</td>
<td>M</td>
<td>Papillary</td>
<td>Thyroid, original</td>
<td>Weak</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>S.J.</td>
<td>65</td>
<td>F</td>
<td>Papillary, follicular variant</td>
<td>Neck, recurrent</td>
<td>Weak</td>
<td>+ve/bone (1)</td>
<td>+ve/bone (2)</td>
</tr>
<tr>
<td>S.S.W.</td>
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<td>F</td>
<td>Papillary, follicular variant</td>
<td>Thyroid, original</td>
<td>Weak</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>K.S.</td>
<td>52</td>
<td>F</td>
<td>Papillary</td>
<td>Neck, recurrent</td>
<td>–ve</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>S.P.K.</td>
<td>44</td>
<td>F</td>
<td>Papillary</td>
<td>Thyroid, original</td>
<td>–ve</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>S.S.M.</td>
<td>25</td>
<td>F</td>
<td>Papillary</td>
<td>Thyroid, original</td>
<td>–ve</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>J.D.</td>
<td>46</td>
<td>F</td>
<td>Papillary</td>
<td>Neck, recurrent</td>
<td>–ve</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>S.S.N.</td>
<td>62</td>
<td>F</td>
<td>Papillary</td>
<td>Thyroid, original</td>
<td>–ve</td>
<td>–ve</td>
<td>–ve</td>
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<tr>
<td>P.S.J.</td>
<td>69</td>
<td>F</td>
<td>Papillary</td>
<td>Thyroid, original</td>
<td>–ve</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>C.S.P.</td>
<td>67</td>
<td>M</td>
<td>Papillary</td>
<td>Neck node, original</td>
<td>–ve</td>
<td>–ve</td>
<td>–ve</td>
</tr>
</tbody>
</table>

PPAR-γ: peroxisome proliferator–activated receptor-gamma; Dx TBS: diagnostic total body scan; RZ: rosiglitazone; post Rx TBS: post–I-131 treatment total body scan; -ve: negative TBS; +ve: positive TBS.

Follicular carcinoma, as well as mixed papillary–follicular tumors had positive TBS, while those with solid/trabecular variant of papillary carcinoma did not have positive TBS. This may imply that different cell types have different responses to RZ. Frohlich et al. (23) studied the effect of TZDs on iodide uptake in transformed thyroid follicular cell lines. They found that TZDs caused an increase in iodide uptake, and different cell lines reacted differently to TZDs. After multiple passages of these cell lines through TZDs, the ability of TZDs to increase iodide uptake was lost. This might also be another explanation for the non-RAI uptake in some types of papillary thyroid carcinoma cells, which are the majority of our patients. Thus, the action of various TZDs on NIS and iodide uptake might or might not be the same. A later study showed that troglitazone also upregulated NIS mRNA in some papillary thyroid carcinoma cell lines (25). Further studies need to be done in papillary thyroid carcinoma using RZ to explore its effect on NIS and iodide uptake. We did not test for the effect of RZ on NIS expression due to the inability to obtain the recurrent tumor tissues post-RZ.

The optimal duration of treatment by RZ is still unknown. We demonstrated that 6 weeks of treatment is adequate to
produce a positive TBS. The optimal time may be even lesser than this, as evidenced in an experiment in vitro (26). Incubation of thyroid carcinoma cells with ciglitazone for only 24 hours caused inhibition of cell growth in vitro. It was observed that the inhibition was time and dose dependent (11,26). This means that if there is more time and more dose exposure to the drug, the more inhibition is seen. On the contrary, repeated exposure to TZDs may also lead to an inverse effect (23). In our study we used the same dose of RZ as normally prescribed for diabetic patients and the same time as we used for TBS preparation. However, the capability of tumor inhibition is not the capability of RAI uptake. Thus, the question of best TZD treatment duration to stimulate I-131 uptake and its mechanism of action (either directly on NIS or on redifferentiation) needs further study.

In humans, there are only two studies that used RZ for treatment trials in patients with high Tg but negative Dx TBS. The first study involved only five patients (27). The result of Dx TBS was negative in four of five cases after 3 months of RZ treatment. In one case, it showed only a faintly positive scan. However, the study did not test PPAR-γ expression. It was concluded that RZ did not restore iodine trapping. The second study was performed in 10 patients (28). Four had positive Dx TBS. The researchers found that there was no difference in the level of PPAR-γ mRNA and protein expression between patients who had RAI uptake and those who did not. However, the study did not examine separately the intensity and the area of staining. Thus, patients with low mRNA or protein expression but high RAI uptake after RZ might have high intensity but small areas of staining, or vice versa. Further, since this study reported data obtained from only a few patients, the conclusions are not conclusive.

Our study also showed that two patients with strong PPAR-γ-positive staining and also positive post Rx TBS had a substantial reduction in Tg levels after RZ and I-131 treatments, while none of the weak PPAR-γ-positive and

**FIG. 3.** Anterior and posterior whole body views of posttherapeutic I-131 total body scan (post Rx TBS) before enrollment (first column), Dx TBS2 (second column), and post Rx TBS after 6 weeks of rosiglitazone (RZ) administration (third column) in three out of six patients who had positive effect of RZ on TBS. (A) Patient P.R. with negative Dx TBS2 and positive post Rx TBS at neck and lungs. (B) Patient S.L. with weakly positive Dx TBS2 at right thigh and two strongly positive foci on post Rx TBS at right hip and thigh. (C) Patient J.L. with weakly positive Dx TBS2 at neck and strongly positive post Rx TBS at neck. (Areas of positive uptake are shown in arrows.)

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