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EDITORIAL

ALARA in rhTSH-stimulated post-surgical thyroid remnant ablation: what is the lowest reasonably achievable activity?

Daniele Barbaro · Frederik A. Verburg · Markus Luster · Christoph Reiners · Domenico Rubello

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For several years now recombinant human TSH (rhTSH) has been approved by the European Medicines Agency (EMEA) for the preparation of differentiated thyroid carcinoma (DTC) patients for radioiodine (^{131}I) ablation of thyroid remnants after surgery. Its effectiveness in patient preparation before ^{131}I ablation has been shown in multiple prospective studies [1–7].

In this editorial we will review the existing literature on the topic of rhTSH-stimulated ^{131}I ablation with emphasis on factors that may influence the success rate of ablation, such as the administered activity, the size of the post-surgical thyroid remnant and the amount of stable iodine present in patients at the time of ablation.

The available studies in the literature differ greatly in the activities of ^{131}I used for ablation as well as the stages of patients eligible for inclusion, although most studies have used fairly uniform criteria for successful ablation. The available studies with their key criteria and results are summarized in Table 1. In this table, it can be seen that in those studies using 1.85 GBq (50 mCi) ^{131}I or more, there is little or no reason to doubt the equivalence of rhTSH to levothyroxine (LT_4) withdrawal for the preparation of ablation, while rhTSH stimulation significantly decreases the whole-body radiation exposure [8]. The effectiveness of ^{131}I ablation using rhTSH, which led to its approval by European and US authorities for this indication, is corroborated by a recent retrospective study of 394 patients in which the short-term clinical recurrence did not differ between subjects prepared by rhTSH or LT_4 withdrawal [9].

For the studies using 1.11 GBq (30 mCi) ^{131}I, the results are more differentiated: whereas the studies by Barbaro et al. [6, 7] did not show a significant difference in the rates of successful ablation between patients prepared with rhTSH and LT_4 withdrawal, Pacini et al. [5] did find a considerable difference. Some speculation is possible about the reason for the difference found by Pacini et al.; the most likely explanation is that the administration of the ablative ^{131}I activity on the second day after the last administration of rhTSH is too late. Based on a large international trial [10] it was recommended in the registration that ^{131}I should be administered on the first day after the last rhTSH injection.

The exact activity that needs to be administered in order to achieve successful ablation is still a subject of debate [11]. There are only a few studies comparing the success rate of ablation during classic LT_4 withdrawal and none that compare different activities under rhTSH stimulation. Those studies which are available, such as the one by Bal et al. [12], seem to indicate that there is no real increase in ablation success rates for activities exceeding 1.85 GBq (50 mCi), albeit under classic withdrawal conditions.

D. Barbaro
Endocrinology Unit, General Hospital of Livorno,
Livorno, Italy

F. A. Verburg · C. Reiners
Department of Nuclear Medicine, University of Würzburg,
Würzburg, Germany

M. Luster
Department of Nuclear Medicine, University of Ulm,
Ulm, Germany

D. Rubello (✉)
Department of Nuclear Medicine, PET Centre, Radiology,
Medical Physics, 'Santa Maria della Misericordia' Hospital,
Viale Tre Martiri 140,
45100 Rovigo, Italy
e-mail: domenico.rubello@libero.it

Table 1 An overview of prospective studies on rhTSH ablation, ordered by activity used for ablation. All studies were rhTSH vs withdrawal unless otherwise noted

Study	No. of patients (controls)	Stages included in trial	^{131}I administration on day after last rhTSH injection	^{131}I activity used for ablation	Criteria for successful ablation	% Successful ablation in patients (controls)
Robbins et al. [1]	10 (0)	I-IV	1	1.11–9.25 GBq, dosimetry based	No visible ^{131}I uptake	100% (NA)
Pacini et al. [2]	32 (28)	pT1-4 N0-1 M0	1	3.7 GBq	No visible ^{131}I uptake	75% (86%), p=NS
					<0.1% thyroid uptake	100% (100%)
Pilli et al. [3]	72 (0)	pT1-4 N0-1 M0	1	1.85 GBq vs 3.7 GBq	TG < 1 nmol/l	1.85 GBq: 78.9%; 3.7 GBq: 66.6%, p=NS
					No visible ^{131}I uptake	Both groups 88.9%
Chianelli et al. [4]	21 (21)	pT1 N0	1	2.0 GBq	TG < 1 nmol/l	85% (90%), p=NS
					No visible ^{131}I uptake	90.5% (95.2%), p=NS
Pacini et al. [5]	42 (30)	pT1-4 N0-1 M0	2	1.11 GBq	No visible ^{131}I uptake	54% (84%), p<0.01
Barbaro et al. [6]	16 (19)	I-II	1; LT_4 was stopped 4 days before ^{131}I	1.11 GBq	TG < 1 nmol/l	87.6% (79.1%), p=NS
					No visible ^{131}I uptake	88.7% (75.0%), p=NS
Barbaro et al. [7]	52 (41)	I-II	1; LT_4 was stopped 4 days before ^{131}I	1.11 GBq	TG < 1 nmol/l	86.5% (78.0%), p=NS
					No visible ^{131}I uptake	76.9% (75.6%), p=NS

TG thyroglobulin

However, in the UK and in France two major trials are currently ongoing, both of which contain an rhTSH arm, which aim to determine what activity is required for a successful ^{131}I ablation; the first results of these trials are expected to emerge later in the year 2010. Even if these trials may not be able to provide the definitive and nuanced answer to the question on how high the ablative ^{131}I activity should be precisely, they will certainly be able to give a good sense of the range for further detailed research.

The second major consideration in ^{131}I ablation is the size of the thyroid remnants. This parameter strictly depends on the true extent of the total thyroidectomy, which in turn largely depends on the skill and experience of the surgeon performing the procedure, as well as the concomitant thyroid pathology such as goitre.

Measuring the size of the thyroid remnant remains a difficult matter, certainly in the immediate post-operative period where tissue oedema prevents the acquisition of a clear image and accurate measurements. A post-surgery ultrasound probably represents the easier diagnostic tool to evaluate the size of the post-operative thyroid remnants and should be part of any post-surgical evaluation. Ideally (though in clinical practice this is often difficult as ablation is often scheduled ca. 4 weeks after surgery) it should not be performed before 40–60 days after surgery to allow the post-surgical oedema to recede. Nonetheless volume estimation of small thyroid remnants remains difficult and imprecise, which in turn makes an meaningful thyroid remnant dosimetry all but impossible.

A final important point that deserves attention when trying to use lower activities of ^{131}I is the potential role of the iodine metabolism. Some important differences exist in this regard between LT_4 withdrawal and rhTSH stimulation. The iodine clearance in euthyroid state is considerably higher than in hypothyroidism [8, 13–16] for example. Therefore the biological whole-body half-life of ^{131}I is shorter under rhTSH stimulation than it is under withdrawal. In contrast it is also known that the intrathyroidal ^{131}I half-life is longer during rhTSH stimulation than during LT_4 withdrawal [8, 16, 17]. This can be explained by the relatively short duration of the rhTSH stimulus, which only results in a modest secretion of thyroid hormone-bound radioiodine. The ^{131}I residence time between rhTSH stimulation and LT_4 withdrawal in normal cells does not differ however, as the thyrocytes' ^{131}I uptake tends to be lower after rhTSH stimulation than during LT_4 withdrawal [8, 16].

Physiology teaches us that ^{131}I uptake is, at least in part, inversely related to iodine intake and the whole-body iodine pool, as stable iodine in a pharmacological sense works as a competitive ^{131}I inhibitor. For this reason low-iodine diets have been employed for many years in preparing patients for ^{131}I ablation [18–21]. Considering that, as stated before, iodine uptake tends to be lower under rhTSH than under withdrawal, it seems that in the case of rhTSH-stimulated ablation the need for reducing the whole-body stable iodine pool is even more important in order to maximize the therapeutic effect of the longer iodine retention under rhTSH. This may be especially true in areas with a high nutritional iodine intake. Consequently it is conceivable that the lower the ablative ^{131}I activity used, the more important the reduction of stable iodine becomes. The studies by Barbaro et al. [6, 7], who performed ablation under rhTSH stimulation with an activity of only 1.1 GBq after patient preparation with a stringent diet as well as a so-called mini-withdrawal (i.e. the discontinuation of LT_4 for 4 days before ^{131}I administration as it is a source of stable iodine), seem to prove that it is possible to effectively ablate patients using only 1.11 GBq when paying attention to the reduction of the whole-body iodine pool; the ablation success rates in the studies by Barbaro et al. were comparable with those in studies which used a higher ablative ^{131}I activity. Furthermore, in a recently published study by Barbaro et al. [22] comparing stage-adjusted activities for rhTSH-stimulated ablation as well as several preparation regimes, it was shown that the whole-body pool of stable iodine, as measured by its urinary excretion, could be further reduced significantly by adding furosemide treatment to the preparation regime. In this study, patients pre-treated with furosemide showed a non-significant trend towards a higher success rate.

With only sparse literature to go by, it seems that the role of the reduction of the whole-body stable iodine pool before ablation certainly deserves further study—especially where it comes to measures such as the addition of a mini-withdrawal or furosemide therapy to the patient preparation procedure.

In conclusion, there are still (too) many open questions to definitively answer what activity is the lowest reasonably achievable activity for rhTSH-stimulated ^{131}I ablation. There are however indications in the literature that lower activities of 1.85 GBq or, at least with special preparations such as an LT_4 mini-withdrawal and/or furosemide treatment, even 1.1 GBq are attainable. Whether 1.1 GBq ^{131}I is also sufficient without such extensive patient preparation, or in patients with large thyroid remnants, remains subject to further study.

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