

## INVITED COMMENTARY

## Glucocorticoids and outcome of radioactive iodine therapy for Graves' hyperthyroidism

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Radioactive iodine (RAI) is a well established and very effective method of treatment for Graves' hyperthyroidism (1). RAI is given preferentially after pretreatment with antithyroid drugs to restore euthyroidism, or, especially in mild forms of hyperthyroidism and in young patients, without pretreatment (2). Its effectiveness can be increased by a short adjuvant treatment with lithium carbonate, which allows a prompt control of thyrotoxicosis and an earlier shrinkage of goiter (3).

Why should glucocorticoids be given concomitantly with RAI therapy? One possible reason is the occurrence of radiation thyroiditis, heralded by pain in the anterior neck region after RAI administration. This is a rare event, and non-steroidal anti-inflammatory agents for a few days are usually enough to control this transient phenomenon (1). The most important reason to use glucocorticoids concomitantly with RAI administration is to prevent the possible RAI-associated worsening of Graves' ophthalmopathy (GO). RAI therapy causes GO progression in about 15% of cases, although this event is often transient (4). GO progression after RAI is more likely to occur in patients who already have GO prior to RAI therapy, smoke, have more severe hyperthyroidism and high levels of thyrotropin (TSH) receptor antibody (TRAb), or whose post-RAI hypothyroidism is not promptly corrected by L-thyroxine replacement therapy (5). In these at-risk patients a relatively short course of moderate doses of oral glucocorticoids prevents progression of eye disease and often cures preexisting GO (6).

An important problem, addressed by Jensen *et al.* in this issue of the *European Journal of Endocrinology* (7), is whether the concomitant administration of glucocorticoids may influence the outcome of RAI therapy and reduce its effectiveness. High doses of glucocorticoids have multiple effects on pituitary-thyroid function. These include transient inhibition of TSH secretion, reduced peripheral monodeiodination of thyroxine to triiodothyronine, and a decrease in thyroxine-binding globulin circulating levels (8). These effects are unlikely to affect the outcome of RAI therapy. In addition, glucocorticoids enhance – modestly – urinary clearance of iodide (8); this might somehow decrease recycling of RAI and, thereby, reduce its effectiveness. However,

the demonstration that this is indeed the case is lacking. Interestingly, in FRTL-5 cells, dexamethasone has been shown to decrease sodium iodide symporter (NIS) expression, NIS RNA steady-state levels and iodide accumulation (9). This might provide the basis for a decreased RAI effect owing to glucocorticoid treatment. On the other hand, in prostate cancer cells expressing NIS, dexamethasone enhances the cytotoxic effects of RAI therapy (10). Cytotoxic effects of RAI are related to the formation of reactive oxygen species, which are responsible for DNA damage and ultimately cause cell death. Whether glucocorticoids affect production of reactive oxygen species is controversial, and conflicting results have recently been reported in the literature. While inhibition of intracellular production of reactive oxygen species was shown in platelets (11), glucocorticoid excess induced superoxide production in vascular endothelial cells, thereby contributing to vascular endothelial dysfunction (12). In addition, glucocorticoid treatment did not inhibit cardiac production of reactive oxygen species after reperfusion during conventional cardiac surgery (13); in the same study steroids decreased lipid peroxidation, but did not affect the occurrence of arrhythmias (13).

Thus, experimental data do not provide an unequivocal basis to predict a possible effect, either positive or negative, of glucocorticoids on the outcome of RAI therapy for hyperthyroidism. What do we know from the few clinical studies in which this aspect was evaluated? In a prospective study of 40 patients with Graves' disease, betamethasone, given for 3 weeks before and 4 weeks after RAI therapy, delayed, but did not abolish, the RAI-associated rise in thyroid autoantibody levels, and caused a decrease in total serum IgG (14). At the end of the 12-month follow-up period, 9 out of 20 (45%) betamethasone-treated patients and 17 out of 20 (85%) placebo-treated patients developed hypothyroidism (14). Because the latter is considered a desirable goal of RAI therapy, one may argue that this regimen of glucocorticoid therapy does reduce the effectiveness of RAI therapy. In a study of 31 Graves' patients submitted to RAI therapy, no differences in the outcome of treatment were observed in the subgroup of patients treated with glucocorticoids after RAI administration,

**Table 1** Effect of glucocorticoid therapy on the outcome of radioactive iodine therapy (RAI) for Graves' hyperthyroidism.

Author	Year	Glucocorticoid regimen	Cure rate (Eu + Hypo)
Gamstedt & Karlsson (14)	1991	Pre- and post-RAI	45 vs 85% in patients receiving placebo
Chiovato <i>et al.</i> (15)	1998	Post-RAI	No different outcome compared with patients not receiving steroids
Bartalena <i>et al.</i> (4)	1998	Post-RAI	66 vs 62% in patients receiving RAI alone
Jensen <i>et al.</i> (7)	2005	Post-RAI	60 vs 59% in patients not receiving steroids

Eu, euthyroidism; Hypo, hypothyroidism.

as compared with patients not receiving steroid treatment (15). In our large study of the effects of RAI on GO, the prevalence of permanent hypothyroidism after RAI therapy was superimposable in patients treated with RAI alone (62%) or with RAI followed by glucocorticoid coverage (66%) (4); likewise, treatment failure, i.e. persistent hyperthyroidism, was similar in the two groups (14 and 12%, respectively) (4). The present study by Jensen *et al.* lends further support to the above results by showing that the cure rate (euthyroidism + hypothyroidism) in patients treated with RAI alone or with RAI followed by glucocorticoids was identical (60 and 59%, respectively) (7).

Therefore, available data suggest that post-RAI treatment with glucocorticoids, usually given to prevent GO progression, does not affect the outcome of RAI therapy for hyperthyroidism (Table 1). Accordingly, no increase in the dose of RAI is required. Conversely, pretreatment with glucocorticoids may reduce the effectiveness of RAI therapy and should, therefore, be avoided (Table 1). In conclusion, in patients in whom it is required (smokers with preexisting GO, severe hyperthyroidism, high TRAb titers), glucocorticoid therapy can be safely administered without any fear of compromising the outcome of RAI therapy.

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