HYPERTHYROIDISM

Clin Thyroidol 2020;32:62–64.

Steroids Are Effective for Preventing Post-RAI Graves' Orbitopathy In Those with Graves' Disease of <5 Years' Duration

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Review of: Vannucchi G, Covelli D, Campi I, Curro N, Dazzi D, Rodari M, Pepe G, Chiti A, Guastella C, Lazzaroni E, Salvi M 2019 Prevention of orbitopathy by oral or intravenous steroid prophylaxis in short duration Graves' disease patients undergoing radioiodine ablation: A prospective randomized control trial study. *Thyroid* 29:1828–1833. PMID: 31860407.

SUMMARY

Background

Radioactive iodine (RAI) is known to increase the risk of the development or reactivation of Graves' orbitopathy (GO) (1). Those at the highest risk are cigarette smokers, patients with high serum TSH-receptor antibodies (TRAb) titers and high pretreatment serum T₃ levels, and those whose hypothyroidism after RAI administration is not corrected promptly. Oral steroid prophylaxis has proved to be effective at preventing this adverse outcome in the past (2), but the question of which individuals are the best candidates for such prophylaxis remains under debate (3,4). The impact of the duration of Graves' disease (>5 years versus <5 years) and the activity status of GO (active disease defined as clinical activity scores [CAS] ≥3/7 or inactive disease defined as CAS >4/10) have been considered important elements. Unfortunately, the available literature on this topic is unable to clearly answer these questions, which is what this study (5) aims to address.

Methods

This was a prospective study of patients with Graves' disease who underwent RAI therapy to treat per-

sistent hyperthyroidism after standard antithyroid drug (ATD) therapy. Those with a disease duration of <5 years were randomly assigned to oral or IV glucocorticoids for the prevention of GO development or reactivation. Patients with a duration of Graves' disease of >5 years did not receive steroid therapy and were included in the study as controls.

RAI therapy was administered at a fixed dose of 600 MBq (16 mCi). Steroids were started 48 hours after RAI according to the following protocol: 35 mg/day of prednisone that was tapered off in 10 weeks, or methylprednisolone administered weekly over 4 weeks (500 mg/week for 2 weeks, then 250 mg/week for 2 weeks). The primary outcome was GO reactivation (CAS >3/10) or de novo GO development by 6 months post-RAI therapy, although patients were followed for up to 5 years after the ablative therapy.

Results

A total of 121 patients (99 with GO and 22 without GO) were studied as they received RAI for recurrence of hyperthyroidism after discontinuation of

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ATD therapy. About 80% in each group had preexisting and inactive GO. Fifty patients received IV glucocorticoids, 49 received oral glucocorticoids, and 22 were observed without steroid prophylaxis. There were no new cases of GO detected. Furthermore, none of the patients who received steroid prophylaxis had GO reactivation within 6 months after RAI therapy, but one patient in each group reactivated over the course of follow-up (up to 5 years). One patient in the control group did have GO reactivation following the development of hypothyroidism, but the GO improved when thyroid levels normalized. The duration of Graves' disease, serum TRAb titers, and steroid use did not affect RAI efficacy. Persistent hyperthyroidism was more likely in those with larger thyroid glands. Serum TRAb levels increased as expected, but displayed a

delayed rise in steroid-treated patients. More than 80% of the patients who answered the side-effects questionnaire reported some possible steroid-related symptoms (weight gain, dyspepsia, fatigue, etc.); those treated with oral glucocorticoids were more likely to have such symptoms, as compared with those who received IV glucocorticoids.

Conclusions

The risk of GO induced by RAI therapy can be prevented by steroids in patients with Graves' disease of <5 years' duration. Such therapy might not be necessary in those with Graves' disease >5 years' duration. The known increase in serum TRAb titers following RAI therapy is delayed by steroid prophylaxis, which likely contributes to the reported GO-related benefit.

COMMENTARY

This study is meaningful because long-term ATD therapy is used for an increasing number of patients with Graves' disease (6). As some of these individuals will be switched to RAI therapy, these data demonstrate that in patients with Graves' disease of >5 years' duration, the risk of new GO development or GO reactivation related to RAI treatment is extremely low. Therefore, such patients do not usually need routine steroid prophylaxis. However, they also indicate that, irrespective of the duration of Graves' disease, the risk of GO reactivation is not null, as initially reported (7). The timing of reactivation (12–20 months after RAI therapy in this study) is longer than previously considered.

Serum TRAb levels increased as expected in all groups after RAI therapy, but displayed a 4- to 6-month delayed rise in those treated with prophylactic steroids, consistent with previous reports (1). Thus, GO-related outcomes might be delayed as

well. Whether the addition of selenium to steroids would be able to eliminate the adverse GO risks is unknown.

In patients without GO, this study confirms what Bartalena et al. described in 1998 (2); in their study, none of the 70 steroid-treated patients who did not already have GO had eye changes after RAI therapy. It is also useful to confirm that oral glucocorticoids are equally effective as IV formulations, although the longer oral treatment and its more pronounced side-effect profile needs to be considered in the final choice of steroid for prophylaxis.

Thus, should steroids be given to all RAI-treated patients with Graves' disease of <5 years' duration who do not have existing GO? The risk can be nuanced based on the other known risk factors (e.g., cigarette smoking, high serum TRAb titers, and severe biochemical hyperthyroidism), and thus an

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informed decision incorporating all of these considerations should be made, as also advised by EUGOGO guidelines (3). The conclusions formed by this study apply to patients without GO or those with inactive GO. With regard to those with active GO, the pro-

tection provided by prophylactic steroids is probably adequate for mild GO cases, but for patients with moderate-to-severe disease or optic neuropathy, RAI is best avoided (4).

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