PREVENTION OF ORBITOPATHY BY ORAL OR INTRAVENOUS STEROID PROPHYLAXIS IN SHORT DURATION GRAVES' DISEASE PATIENTS UNDERGOING RADIOIODINE ABLATION: A PROSPECTIVE RCT STUDY.

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Short Title: Radioiodine therapy and Graves' orbitopathy

Key words: Graves' disease, Graves' orbitopathy; Radioiodine, Glucocorticoids, TSH-receptor antibodies

Precis: Prevention of Graves' orbitopathy activation after radioiodine therapy with steroids administered either orally or intravenously to patients with disease duration of less than five years.

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ABSTRACT

Context: RAI is a known risk factor for activation or *de novo* occurrence of Graves' orbitopathy (GO). Several studies demonstrated that GO can be prevented by glucocorticoids (GC) in patients with pre-existing GO. We have previously shown that Graves' disease duration (GDd) <5 years is a risk factor for RAI-induced GO.

Objective: To study the effect of prophylaxis with either oral GC (OGC) or intravenous (IVGC) on GO activation in patients with GDd <5 years with and without pre-existing GO.

Patients and setting: 99 hyperthyroid patients without GO or with pre-existing inactive GO with GDd <5 years were randomized to receive IVGC (N=49) or OGC (N=50) prior to RAI; 22 patients with GDd >5 did not receive steroids and were studied as controls.

Main Outcome Measures: All patients underwent ophthalmological assessment before and 45, 90 180 days and for a 5 year follow-up after RAI. Serum TRAb, thyroid hormones and thyroid volume (TV) were also measured in response to RAI therapy and steroid prophylaxis.

Results: No patient on prophylaxis developed GO after RAI. One woman of the control group, without steroid prophylaxis, and who had a marked elevation of her TSH, showed transient reactivation of GO, that spontaneously improved after restoring euthyroidism. On follow-up at 12 and 20 months after RAI, two patients developed overt optic neuropathy. A smaller TV was associated to a higher prevalence of RAI-induced hypothyroidism. Serum TRAb increased significantly after RAI ($P<0.0001$) but less in patients receiving steroids than in those without prophylaxis at 45 days ($P<0.01$).

Conclusions: The risk of RAI-induced GO can be prevented in all patients with GDd <5 years by steroids. Such treatment may not be necessary in patients with GDd >5 years. The blunting of TRAb elevation after RAI may be related to the prophylactic effect of steroids.

INTRODUCTION

Radioiodine (RAI) ablative treatment for Graves' hyperthyroidism (GD) has been associated with *de novo* occurrence or worsening of GO (1). The development or progression of GO after RAI is thought to be the consequence of radiation damage to the thyrocytes, resulting in release of thyroid antigens and activation of autoimmune reactions directed to the orbit (2). It is well accepted that patients with pre-existing GO who are active smokers, severely hyperthyroid prior to therapy, and with elevated serum levels of TSH-receptor antibodies are at increased risk for the progression of GO after RAI (3). In addition, GO may develop also if post-RAI hypothyroidism is not promptly corrected (4). In 1989, Bartalena et al. showed that systemic oral glucocorticoids (OGC) prevent the exacerbation of GO that may occur after RAI in a proportion of patients with GD who have some degree of ocular involvement before treatment (5). Low-dose OGC prophylaxis has therefore been recommended in recent guidelines (EUGOGO; EUropean Group On Graves' Orbitopathy) for patients undergoing RAI who consider pre-existing GO among the risks of progression or *de novo* development of GO (6). A recent meta-analysis, which included 850 patients submitted to RAI, concluded that OGC are very effective in preventing GO progression in patients with pre-existing GO, whereas randomized studies showing that steroid prophylaxis might be beneficial in patients without pre-existing signs of eye involvement are lacking (7).

Although the mechanism of RAI in triggering GO in patients without pre-existing disease is not clearly understood, *de novo* GO has been associated with cigarette smoking as a risk factor (1, 8). As recently suggested (9), in patients without GO the indication for steroid prophylaxis should be discussed with the patient prior to RAI treatment and based on specific risk factors. To date, there is unfortunately no consensus on either the criteria for selecting patients who may require steroid prophylaxis after RAI or the optimal steroid regimen, as reported in a survey among members of the European Thyroid Association (10). In 2009, a retrospective study on 113 patients submitted to RAI therapy assessed the prevalence of reactivation or *de novo* onset of GO, with or without steroid

prophylaxis administered orally or intravenously (11). GO reactivated in 7.9% and newly occurred in 6.2% of patients, and was significantly more prevalent in patients with GD duration (GDd) less than 5 years. Moreover, intravenous glucocorticoids (IVGC) were shown to be more effective than OGC in preventing GO after RAI.

We have therefore designed the present prospective study in which patients with GDd of less than five years were randomized to receive either oral or intravenous steroid prophylaxis. As controls, we have studied patients with GDd of more than five years, who were not submitted to prophylaxis. The study objective was reactivation of GO or *de novo* occurrence of GO at six months after RAI. Patients were then observed for up to 5 years from RAI administration. In addition to GO activation, other study objectives were the outcomes of RAI therapy in controlling hyperthyroidism, the modifications of circulating TRAb in response to steroid prophylaxis and the impact of side effects, as recorded through a specific questionnaire administered to the patients during the course of steroid therapy.

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PATIENTS AND METHODS

Patients

One-hundred and twenty-one consecutive patients, 93 women and 28 men aged 23-70, mean age (±SE) 47.1 ±1.2 yr, with Graves' disease (GD) and relapsing hyperthyroidism after standard treatment with antithyroid drugs, were seen between July 2009 and July 2012 and studied prospectively and observed until 2017. Ninety-nine patients with pre-existing inactive GO (CAS<4/10) and 22 with no evidence of GO were treated with RAI at the time when hyperthyroidism relapsed with elevated serum free thyroid hormone concentrations not exceeding more than 50% of the normal range, to reduce the risk of post-RAI thyrotoxicosis (Table 1). Exclusion criteria were: the presence of active moderate or severe GO (dysthyroid optic neuropathy), contraindications to glucocorticoids administration, and pregnancy. Patients with GDd shorter than 5 years were randomized to receive prophylaxis with low dose IVGC (n=50) (Group A) or OGC (n=49) (Group B). As controls, we studied 22 patients with GDd of more than 5 years treated with RAI without steroid prophylaxis (Group C; Table 1). All patients were studied prospectively at 45, 90, 180 days after RAI treatment, by testing thyroid function and serum TRAb levels and by performing ophthalmological assessment, which included lid fissure and Hertel measurements, visual acuity and eye motility determination. Soft tissue involvement was graded according to the Color Atlas available at *www.eugogo.eu* (12) Activity of GO was classified by the clinical activity score (CAS) (13). Patients were subsequently observed in our clinic for up to 5 years after RAI administration. The study was registered (EUDRACT number 2009-010632-18) and approved by the Ethics Committee of our Institution and informed consent was obtained from all the patients.

RAI treatment and steroid prophylaxis

All patients underwent a Tc^{99} thyroid uptake 48 hours before administration of a therapeutic dose of radioiodine. 131-I was administered at a fixed dose of 600 MBq, the maximum dose allowed for

133 out-patients according to the national legislation. In all patients, thyonamides were discontinued 5-
134 10 days before RAI therapy.
135 Steroid prophylaxis was begun 48 hour after administering RAI. OGC prophylaxis consisted in the
136 administration of a fixed starting dose of 35 mg/day of prednisone tapered off in 10 weeks with a
137 cumulative dose of 1.540 g IVGC were administered with two doses of 500 mg/week for the first
138 two weeks and two of 250 mg/week for the last two weeks, with a cumulative dose of 1.500 g of
139 methylprednisolone. In all patients, a pump proton inhibitor was administered throughout the period
140 of steroid prophylaxis, to prevent gastric bleeding.

141 **Biochemical analysis and clinical assessment**

142 Serum FT4, FT3 and TSH concentrations were measured using an electrochemiluminescent
143 immunoassay (ECLIA, Roche Diagnostics) and reference ranges were 8-17 pg/ml, 2-5 pg/ml and
144 0.26-5.2 mU/L, respectively. Hypothyroidism was defined as a TSH >3.5 mU/L. The value of 3.5
145 mU/L is the one we chose to begin LT4 replacement after RAI, in order to prevent GO progression
146 due to hypothyroidism. Serum TSH receptor antibodies (TRAb) were measured as TSH binding
147 inhibitory immunoglobulins, using a 2nd generation TRAK human lumitest (Thermofisher, AG,
148 Henningsdorf/ Berlin, Germany) (reference value <1.5 U/L). In patients undergoing steroid
149 prophylaxis, serum glucose, aminotransferases and gamma-glutamyltransferase were measured
150 before RAI and at the end of steroid administration and expressed as U/L. Serology for HBV and
151 HCV viruses was also tested at baseline. At baseline, all patients were investigated for smoking
152 habits. Thyroid volume (TV) was measured in all patients by thyroid ultrasound at baseline and at
153 180 days after RAI by the same operator. All patients undergoing steroid prophylaxis were
154 administered a questionnaire on the side effects of treatment, which recorded pain in the thyroid
155 region of the neck, asthenia, insomnia, gastritis, hypertension, weight gain and diffuse myalgias.

156 **Study endpoints**

The primary endpoint of the study was the reactivation or *de novo* occurrence of GO, assessed with a CAS ≥ 4/10, in patients with pre-existing or absent GO, respectively. The secondary endpoints were the outcome of hyperthyroidism after RAI and its relationship with steroid prophylaxis, the change in thyroid volume after RAI, and the relation between the modality of steroid administration and eventual adverse effects. We also studied the changes of serum TRAb after RAI and in relation to steroid prophylaxis.

Statistical analysis

All values are expressed as mean ±SE. Analysis by $\chi 2$ test or Mann-Whitney test was applied as appropriate and performed using SPSS 8.0 for Windows. Significance was defined as $P < 0.05$.

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RESULTS

Occurrence of GO after RAI

The clinical and immunological baseline characteristics of all patients are shown in Table 1. There were no differences in age, prevalence of smokers, Tc^{99} uptake and titers of serum TRAb in the groups of patients of the study. Pre-existing inactive GO was present in 82 out of 99 (82.8%) patients undergoing steroid prophylaxis (Groups A-B) and 17 of 22 (77%) of those not receiving steroids (Group C; Table 1). The distribution of patients with or without pre-existing GO was not different in either group of steroid prophylaxis or the control group without prophylaxis (P=NS). Patients with pre-existing GO or without GO were not different in terms of the prevalence of smokers and the presence of serum TSH receptor antibodies (Table 1). None of the patients receiving steroid prophylaxis had reactivation or a *de novo* occurrence of GO at six months after RAI administration (Table 3). In addition, the effect of oral or intravenous steroid administration was not different in preventing GO after RAI. One woman, not submitted to steroid prophylaxis (Group C), had transient GO reactivation 90 days after RAI which occurred when the patient rapidly became markedly hypothyroid (TSH 70 mU/L). GO spontaneously improved after restoring euthyroidism.

During follow-up, two patients developed acute dysthyroid optic neuropathy (DON) (Table 2). Both patients had pre-existing GO and received steroid prophylaxis (one OCG and one IVGC). DON developed at 12 months after RAI in a woman who remained hyperthyroid and eventually required a second cycle of RAI. The second patient developed DON at 20 months of follow-up in the contralateral eye to the one previously affected by GO. In both patients there were subclinical signs of mild inflammation throughout the observation period (CAS 2-3), but not unequivocal evidence of optic nerve involvement.

Analysis of parameters influencing the outcome of RAI in controlling hyperthyroidism

Only 14 patients had a slight elevation of serum FT3 concentrations (mean 5.8±0.7 pg/ml). Overall, RAI was equally effective in inducing hypothyroidism whether the patients received steroid prophylaxis (81/99, 91%) or not (18/22, 81.8%; P=NS) (Table 3), and no difference was found in the time of occurrence of hypothyroidism (P=NS). L-T4 therapy was promptly started when TSH was >3.5 mU/L. Ten patients had persistent hyperthyroidism six months after RAI and among them, eight required additional antithyroid treatment. GD duration did not influence the occurrence of hypothyroidism after RAI in either group of patients (P=NS) or controls (P=NS). Mean basal TV was 18.9±10.9 ml in cured patients compared to 32.7±16.5 ml in subjects who were not cured (Table 3). A decreased TV was significantly associated with a higher prevalence of RAI-induced hypothyroidism in any group of patients (group A and B, P=0.0001, group C, P=0.032), although the magnitude of TV reduction was not different among groups (P=NS).

Relationship between of serum TRAb levels and RAI

As expected, higher basal serum TRAb levels were detected in patients with larger TV (P=0.046; not shown), but they did not differ between patients receiving steroid prophylaxis or not, nor between cured and not cured patients (Table 3; P=NS). Moreover, basal serum TRAb levels in patients who became hypothyroid at 45 days did not differ from those of patients who remained hyperthyroid (not shown; P=NS).

The changes of serum TRAb levels after RAI were studied prospectively to seek a possible relationship with GO reactivation or with steroid prophylaxis. Basal serum TRAb levels were not different in the three groups of patients (Table 1; P=NS) and increased significantly after RAI administration (P<0.0001; Figure 1), as expected. The increase was observed in all groups of patients and were independent of the route of steroid administration. At 45 days after treatment, patients undergoing steroid prophylaxis had significantly lower serum TRAb levels (about 1/3) than those not receiving steroids (Figure1; P=0.01), and a delayed TRAb peak at 180 days.

Side effects of RAI therapy

Sixty-one of 99 patients (61.6%) responded to a questionnaire on side effects of steroid prophylaxis. Twenty-four of 30 (80%) and 26 of 31 (84%) patients receiving OGC and IVGC, respectively, reported at least one symptom such as weight gain, mood disorders and asthenia, with no differences between the route of steroid administration (P=NS). Interestingly, insomnia and gastric symptoms were more frequently reported by patients receiving OGC than IVGC (18 vs 8, P=0.035 and 14 vs 3, P=0.008, respectively).

DISCUSSION

Systemic OGC have been used to prevent the exacerbation of GO after RAI therapy for almost three decades (5), especially in patients with GD who have pre-existing GO. When planning for RAI ablation in patients with GD, the possibility of predicting which patients are at risk for the reactivation or *de novo* development of GO would limit the use of steroid prophylaxis to a specific set of patients. Until now, the choice has been to treat patients with pre-existing GO and with recognized risk factors for GO reactivation, such as smoking and elevated serum TRAb prior to therapy (7, 9). The question that remains unanswered is whether patients without GO undergoing RAI have such a negligible risk of developing GO to avoid prophylaxis or, alternatively, if steroid prophylaxis should be cautiously undertaken in all patients (14). This approach could also be justified based on the data of Lai et al. who suggested that even very low doses of prednisone (0.1-0.2 mg/Kg bw) tapered off in six weeks may be appropriate (15). The present study was designed to confirm that GD duration may be an additional risk factor for GO activation, consistently with previous retrospective findings by our group (11) who found a significantly greater proportion of GO reactivation in patients with recent onset hyperthyroidism (less than 5 years) than in those with disease of longer duration.

In the study presented here, we administered a course of prophylactic steroid therapy in all patients with GDd <5 years and did not observe reactivation or *de novo* occurrence of GO. Control patients, which have a disease duration of more than five years, and not receiving prophylactic steroids, also did not activate or develop GO. Reasons for an increased risk of GO activation in patients with more recent disease are the presence of larger lymphocytic infiltrates in the thyroid (16, 17) and in the orbital tissues (18-20) giving an increased susceptibility for antigenic stimulation. In contrast, patients with long standing disease, stable euthyroidism and burnt out orbitopathy are less likely to harbor lymphocytes in the target tissues. In a recent meta-analysis,

Shiber et al. (7) reported that, while steroid prophylaxis has been shown to be effective in preventing reactivation of GO in patients with pre-existing inactive GO, there are still inconclusive data on the effect of steroids in preventing *de novo* occurrence of GO. Factors that have been known to confer risk for GO activation are elevated serum TRAb levels (12, 21, 22), cigarette smoking (23), severe hypothyroidism after RAI (4), the degree of pre-RAI T3 elevation (24), and pre-existing active GO (25). In the study of Tallstedt et al. (24) an increased risk of developing GO was observed in hyperthyroid patients with more significant serum pre-treatment concentrations of total T3 and treatment with RAI. According to the interpretation of these authors, higher serum T_3 concentrations may indicate more severe immunologic reactivity that predispose patients to Graves' orbitopathy. Since in this study patients with or without pre-existing GO did not differ for known risk factors for GO activation, prophylactic steroids were used in patients with disease duration <5 years, who were considered at increased risk of developing or activating GO than those with duration >5 years. The lack of GO activation observed in both patient groups, suggests that we can confidently prevent GO with low-dose steroids even in patients without pre-existing GO and a short duration of disease. This prospective randomized study also shows that oral and intravenous steroid prophylaxis are equally effective in preventing the occurrence of GO after RAI therapy, whether patients had pre-existing or no GO. Randomization of patients to receive OGC or IVCG, with an equivalent total cumulative dose of steroids, did not significantly affect the study outcome, therefore not confirming the better efficacy of IVGC shown in a previous retrospective study (11).

We followed patients for five years after RAI because the study outcome at 6 months might have missed possible late reactivations of GO. The 5 year long follow-up after RAI ablation did not show additional patients with activation or *de novo* occurrence of GO, with the exception of two patients who developed DON, possibly present subclinically at the time of RAI. This did not overtly manifest until 12 and 20 months after RAI, respectively, thereby making it more likely to be related to the natural course of the disease than RAI therapy itself. At the time of the diagnosis of DON, one patient was euthyroid on L-T4 with undetectable serum TRAb, the other patient had very low

298 titers of serum TRAb, became euthyroid and responded to high doses steroids without requiring
299 surgical orbital decompression. In our cohort of patients we did not observe any influence of
300 smoking on either GO activation or on the outcome of hyperthyroidism, as the number of smokers
301 was not significantly different in the patient groups. When treating Graves' hyperthyroidism, a
302 resulting prolonged or uncontrolled hypothyroid state is known to adversely affect GO (25),
303 especially after RAI (26). Perros et al. (4) have reported that RAI is not associated with GO
304 deterioration when post-RAI hypothyroidism is prevented by early administration of L-thyroxine.
305 In this study, L-T4 therapy was promptly initiated when the serum TSH was > 3.5 mU/L, but one
306 woman, who missed the 45 day follow-up visit, presented at 90 days after RAI with moderately
307 active GO and a marked elevation of her TSH. GO spontaneously resolved after restoring
308 euthyroidism one month later.
309 RAI was effective in controlling hyperthyroidism in about 80% of patients. Neither GD duration,
310 nor pre-treatment serum TRAb levels showed a relation with the response rate. Steroid prophylaxis
311 for GO did not affect the outcome of hyperthyroidism after RAI. These results are similar compared
312 to a previous study by Jensen et al. (27), in which steroid therapy was commenced before
313 administering RAI. The efficacy rate was lower (60%), probably because the mean I-131 activity
314 administered was lower (376 MBq vs 600 MBq) (28). Thyroid volume has been found as the only
315 parameter that influenced the efficacy of therapy, and smaller goiters have been associated with a
316 higher rate of post-RAI hypothyroidism. This finding may be explained by the administration of a
317 fixed dose of RAI that may have been insufficient for larger goiters, if compared to a calculated
318 dose that takes into account the iodine uptake and the thyroid volume (28).
319 It has been shown that TRAb may play a major role in the worsening of GO and that their titers
320 increase about 4-5 fold at 3 months after RAI treatment (21). In this study, we could confirm that
321 serum TRAb levels increase after RAI, but significantly less in patients submitted to steroid
322 prophylaxis when compared to those not receiving steroids. In particular, steroids appear to blunt
323 the increase of serum TRAb at 45 days and to delay it at 180 days. In particular, in control patients

the increase of serum TRAb levels after RAI reached a peak at 45 days, whereas in those submitted to prophylaxis the peak was at 180 days. This protective effect of steroids may play a role in the prevention of GO relapse after RAI therapy although there may be other mechanisms (reduced antigen release, reduce cytokine secretion) that may explain or contribute to this phenomenon (29). Lastly, patients treated with OGC had a slightly higher incidence of side effects, such as insomnia and gastritis, despite the use of proton pump inhibitors throughout the course of steroid prophylaxis (30). This finding suggests that IVGC may be preferable to avoid the more relevant untoward effects related to the prophylactic therapy with steroids, although the intravenous route of steroid administration requires in-hospital medical monitoring and loss of few days of work. A limitation of this study is that we did not study a group of patients with GDd <5 years without prophylaxis, based on previous retrospective work (11). We acknowledge that a proportion of patients who do not receive steroids, may not develop GO after RAI.

In conclusion, RAI treatment is effective and safe for Graves' hyperthyroidism in patients with and without pre-existing inactive GO. GDd < five years is confirmed to be a useful criterion to select patients for steroid prophylaxis after RAI with the aim to prevent activation or *de novo* occurrence of GO. Such prophylactic low dose steroids does not seem to prevent progression of pre-existing GO to DON in a very small number of patients due to the natural disease course and unrelated to RAI therapy. Steroid prophylaxis, at a cumulative dose of 1.5 g, is effective independently of the route of administration. A better safety profile of IVGC suggests that this modality of prophylaxis may improve patient compliance.

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452 **FIGURE LEGEND**

453 **Figure 1**. Changes of serum TRAb levels in response to RAI therapy in patients undergoing OGC

454 prophylaxis (A), IVGC (B) or no prophylaxis (C). A and B vs C at 45 days $P<0.01$ (ANOVA)

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