Continuation of Amiodarone Delays Restoration of Euthyroidism in Patients with Type 2 Amiodarone-Induced Thyrotoxicosis Treated with Prednisone: A Pilot Study

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Context: Type 2 amiodarone-induced thyrotoxicosis (AIT) is a destructive thyroiditis usually responsive to glucocorticoids. Whether continuation of amiodarone affects treatment outcome is unsettled.

Objective: The objective of the study was to compare the outcome of glucocorticoid treatment in type 2 AIT patients who continued or withdrew amiodarone.

Design: This was a matched retrospective cohort study.

Setting: The study was conducted at a university center.

Patients: Eighty-three consecutive patients with untreated type 2 AIT participated in the study. After matching with patients continuing amiodarone (AMIO-ON, n = 8), patients interrupting amiodarone were randomly selected in a 4:1 ratio (AMIO-OFF, n = 32).

Intervention: All patients were treated with oral prednisone. Patients whose thyrotoxicosis recurred after glucocorticoid withdrawal were treated with a second course of prednisone.

Main Outcome Measure: Time and rate of cure were measured.

Results: Median time to the first normalization of serum thyroid hormone levels did not significantly differ in AMIO-ON and AMIO-OFF patients (24 and 31 d, respectively; $P = 0.326$). Conversely, median time for stably restoring euthyroidism was 140 d in AMIO-ON patients and 47 d in AMIO-OFF patients (log rank, $P = 0.011$). In fact, AIT recurred in five of seven AMIO-ON patients (71.4%) and in only three of 32 AMIO-OFF patients (9.4%, $P = 0.002$), requiring readministration of prednisone. One AMIO-ON patient never reached thyroid hormone normalization during the study period. Factors associated with glucocorticoid failure were thyroid volume and amiodarone continuation.

Conclusions: Prednisone restores euthyroidism in most type 2 AIT patients, irrespective of amiodarone continuation or withdrawal. However, continuing amiodarone increases the recurrence rate of thyrotoxicosis, causing a delay in the stable restoration of euthyroidism and a longer exposure of the heart to thyroid hormone excess. **(*J Clin Endocrinol Metab* 96: 3374–3380, 2011)**

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Abbreviations: AIT, Amiodarone-induced thyrotoxicosis; CFDS, color-flow Doppler sonography; CI, confidence interval; FT3, free T_3; FT4, free T_4; NTV, normalized thyroid volume; RAIU, radioactive iodine uptake; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TRAb, TSH receptor antibody; UIE, urinary iodine excretion.

Type 2 amiodarone-induced thyrotoxicosis (AIT) is a destructive thyroiditis that usually develops in a normal thyroid gland (1). It is the most frequent form of AIT (2). Diagnosis of type 2 AIT relies on the absence of thyroid hyperfunction in the presence of circulating thyroid hormone excess (1). Typical findings are low thyroidal radioactive iodine uptake (RAIU) values (particularly in regions with moderate iodine deficiency, whereas in it may be low in both type 1 and type 2 in iodine sufficient regions), the absence of increased thyroidal vascularity at color-flow Doppler sonography (CFDS), and the absence of circulating thyroid-directed autoantibody (1, 3–7). Based on its pathogenic mechanism, type 2 AIT is usually treated with glucocorticoids to accelerate recovery of the damaged gland (1–4). Response to thionamides, which inhibit thyroid hormone synthesis but do not affect the destructive process, is poor to absent (8).

Recent questionnaire-based surveys among expert thyroidologists have confirmed that, in clinical practice, glucocorticoids are the first-line treatment for type 2 AIT (9–12). Cure time may, however, differ, depending on severity of thyrotoxicosis and volume of the thyroid (13). In this regard, it should be emphasized that prompt restoration of euthyroidism is warranted because thyrotoxicosis is harmful for the underlying cardiac disorder and associated with an increased mortality (14). An unsolved question is whether amiodarone therapy should be discontinued when AIT develops. Information is limited, although few reports suggested that the final outcome of AIT apparently does not change whether amiodarone is continued or withdrawn (15, 16).

The aim of this matched retrospective cohort study was to evaluate the impact of amiodarone continuation or withdrawal on the restoration of euthyroidism in type 2 AIT patients treated with oral prednisone. Results demonstrate that amiodarone continuation delays restoration of stable euthyroidism, thus causing a longer exposure to thyroid hormone excess.

Materials and Methods

Study design

This was a matched, retrospective, cohort study comparing the effect of amiodarone continuation or withdrawal on the cure rate and cure time of type 2 AIT patients treated with glucocorticoids. We retrospectively identified 83 patients with type 2 AIT referred consecutively from January 2003 to December 2008 to the Department of Endocrinology of the University of Pisa. The study was conducted using data on patients derived from a prospectively collected database. Data were obtained by the clinical report of each patient.

Patients were divided into two groups: 1) the AMIO-ON group, in which amiodarone treatment had been continued during glucocorticoid therapy; and 2) the AMIO-OFF group, in which amiodarone treatment had been withdrawn after the diagnosis of thyrotoxicosis and not reinstituted until the restoration of euthyroidism. Patients whose thyrotoxicosis recurred after glucocorticoid discontinuation were treated with a second course of prednisone until euthyroidism was achieved.

The AMIO-OFF group was matched with the AMIO-ON group according to sex, age, and the baseline variables with a major impact on the cure-time [serum free T_4 (FT4) concentrations and the estimated thyroid volume normalized by the body surface area (17)]. After matching, AMIO-OFF patients were randomly selected in a 4:1 ratio to the AMIO-ON patients (n = 8).

Subjects

The study included 40 patients with type 2 AIT [35 men, five women; mean (±SD) age 66 ± 11 yr, range 46–86 yr]. Diagnosis of AIT was based on clinical grounds (signs and symptoms of thyrotoxicosis) and laboratory findings, including increased serum free T_3 (FT3) and FT4 concentrations, undetectable serum TSH levels, and increased urinary iodine excretion (UIE). Diagnosis of type 2 AIT was based on the following criteria (1): normal or slightly increased thyroid volume without relevant nodules (≥1 cm) at conventional ultrasonography, absent hypervascularity at CFDS, absence of circulating thyroid-directed autoantibody [antithyroglobulin (TgAb), antithyroid peroxidase (TPOAb), anti-TSH receptor (TRAb)], and low/undetectable RAIU values (<5% at 24 h). Duration of amiodarone therapy ranged from 4 to 156 months (mean ± SΔ, 37 ± 26 months, median 31 months), and the cumulative dose of amiodarone ranged from 24 to 677 g (mean ± SΔ, 198 ± 144 g, median 154 g) in the whole group of patients included in the study.

The ethical board of our department approved the study.

Treatment

It is our policy to stop amiodarone therapy if this is feasible from a cardiological point of view. However, eight patients continued amiodarone therapy in keeping with cardiologist's recommendations. The underlying cardiac abnormalities are shown in Table 1. All patients were treated with oral prednisone (starting dose 0.5 mg/kg · d). The drug was gradually tapered (0.1

TABLE 1. Indications for amiodarone therapy and underlying heart diseases in the study group

	Patient groups	
	AMIO-ON (n = 8) (%)	AMIO-OFF (n = 32) (%)
Indications		
Atrial fibrillation	2 (25)	21 (66)
Atrial flutter		2 (6)
Supraventricolar tachycardia		2 (6)
Supraventricular arrhythmia		3 (9)
Ventricular tachycardia	3 (38)	4 (13)
Ventricular fibrillation	3 (38)	
Underlying heart disease		
Ischemic heart disease	6 (75)	11 (34)
Valvular heart disease		1 (3)
Dilated cardiomyopathy	2 (25)	2 (6)
Hypertrophyic cardiomyopathy		5 (16)
Normal		13 (41)

mg/kg every 7–15 d) and withdrawn after achieving euthyroidism. Patients with recurrence of thyrotoxicosis underwent a second course of prednisone.

Study period and definition of cure

Serum FT4, FT3, and TSH concentrations were measured at 1-wk intervals for the first 3 months and then every month for at least 1 yr. Cure of thyrotoxicosis was defined by: 1) persistent euthyroidism (normalization of both serum FT4 and FT3 levels and TSH concentrations at least 6 months after glucocorticoid withdrawal); and 2) permanent or persistent hypothyroidism (when serum TSH concentrations remained higher than normal at least 6 months after glucocorticoid withdrawal), as previously reported (8). Thyrotoxicosis recurrence was defined by increased serum FT4 and FT3 concentrations at any time during glucocorticoid therapy or within 6 months after prednisone withdrawal. Follow-up lasted 1 yr including the treatment period. To confirm permanent or persistent euthyroidism or hypothyroidism, patients were followed up further for the months needed to complete the 6-month period after glucocorticoid withdrawal.

Assays

Serum FT4, FT3 (Vitros Immunodiagnostics, The Broadway, Amersham, Bucks, UK), TSH (Immulite 2000, third generation TSH; Diagnostic Products Corp., Los Angeles, CA), thyroglobulin (Immulite 2000; Diagnostic Products Corp.), TRAb (TRAK human; Brahms, Hennigsdorf, Germany), TgAb (AIA-Pack TgAb; Tosoh, Tokyo, Japan), and TPOAb (AIA-Pack TPOAb; Tosoh) were assayed by commercial kits. Normal values in our laboratories are as follows: FT4, 7–17 pg/ml (9.0–22.0 pmol/liter); FT3, 2.7–4.5 pg/ml (4.2–7.0 pmol/liter); TSH, 0.4–3.4 mU/liter; TRAb, less than 1 U/liter; TgAb, less than 1 U/ml; and TPOAb, less than 1 U/ml.

Urinary iodine excretion

Morning random urinary samples were collected for iodine measurements using an autoanalyzer apparatus (Technicon, Rome, Italy). Median UIE in our area is 110 μg/liter.

Conventional and color-flow Doppler sonography

Thyroid volume was measured by ultrasonography and calculated by the ellipsoid model (width $\times$ length $\times$ thickness $\times$ 0.52 for each lobe) as previously described (18). Thyroid volume was normalized by body surface area, using the following formula [body surface area (square meters) = $\sqrt{}$ height (centimeters) $\times$ weight (kilograms)/3600] (17); normal values in our areas are 3.5–13 ml/m^2. The CFDS was performed as previously reported (8).

Thyroidal RAIU

Thyroidal RAIU was measured 3 and 24 h after the administration of a tracer dose (50 μCi) of ^{131}I. The normal 3- and 24-h RAIU values in our area are 10–20% and 30–45%, respectively.

Statistical analysis

Data were expressed as mean $\pm$ SD or percentage. At baseline, the difference in demographic, clinical, and pathological features of the AMIO-ON and AMIO-OFF groups were evaluated using Fisher's exact test and ANOVA or Mann-Whitney test for categorical and continuous variables, respectively.

The nonhealing curves were estimated using the Kaplan-Meyer method. Healing was considered as the outcome and the time to healing as time. The statistical comparison between curves was performed using the log-rank test. The Fisher's exact test was used to compare the final nonhealing rates at 1 yr in the two groups. A survival analysis by the Cox proportional hazards

TABLE 2. Clinical and biochemical features of the study groups

	Patient groups		
	AMIO-ON (n = 8)	AMIO-OFF (n = 32)	
Variables	Mean $\pm$ SD	Mean $\pm$ SD	*P*
Sex (female/male)	1/7	4/28	
Age (yr)	64.5 $\pm$ 10	67 $\pm$ 12	0.579
Weight (kg)	72.6 $\pm$ 11.8	73.6 $\pm$ 13.7	0.842
Height (cm)	169.2 $\pm$ 8.2	171.9 $\pm$ 10.1	0.487
BMI	25.2 $\pm$ 3	24.7 $\pm$ 3.1	0.685
FT4 (pg/ml)	40.1 $\pm$ 12.6	39.8 $\pm$ 12.5	0.955
FT3 (pg/ml)	8.5 $\pm$ 5.3	9.0 $\pm$ 5.4	0.831
TSH (mU/liter)	$<$0.01	$<$0.01	1.000
UIE	17559 $\pm$ 9319	7754 $\pm$ 5236	0.020
Third hour RAIU (%)	1.38 $\pm$ 0.67	1.37 $\pm$ 0.89	0.970
24th hour RAIU (%)	0.68 $\pm$ 0.20	0.87 $\pm$ 0.49	0.109
TV (ml)	19.7 $\pm$ 8.2	18.0 $\pm$ 6.1	0.519
NTV (ml/m^2)	10.4 $\pm$ 3.7	9.5 $\pm$ 2.6	0.412
Thyroglobulin (ng/ml)	121.7 $\pm$ 216.9	123.0 $\pm$ 148.6	0.985
Duration of amiodarone treatment (months)	32.7 $\pm$ 20.4	38.1 $\pm$ 27.2	0.604
Cumulative dose of amiodarone (g)	179.2 $\pm$ 108.5	202.8 $\pm$ 153.6	0.685
Recurrence of hyperthyroidism (yes/no)	5/2	3/29	$<$0.001

Data are expressed as mean $\pm$ SD. Normal values in our laboratory are a follows: FT4, 7–17 pg/ml; FT3, 2.7–4.5 pg/ml; TSH, 0.4–3.4 mU/liter; third hour and 24th hour RAIU, in our area, 15–30 and 30–45%, respectively. To convert serum FT4 and FT3 values from picograms per milliliter to picomoles per liter, multiply by 1.29 and 1.54, respectively. NTV was obtained by dividing thyroid volume (TV) by body surface area [the latter calculated using the Mosteller's formula (see *Materials and Methods*)]; normal values in our area are as follows: 3.5–13 ml/m^2; third- and 24th-hour RAIU: third- and 24th-hour thyroidal radioiodine uptake. All patients had undetectable serum TSH, undetectable TgAb, TPOAb, TRAb, color-flow Doppler sonography pattern 0, in keeping with the definition of type 2 AIT given in *Materials and Methods* (see text). BMI, Body mass index.

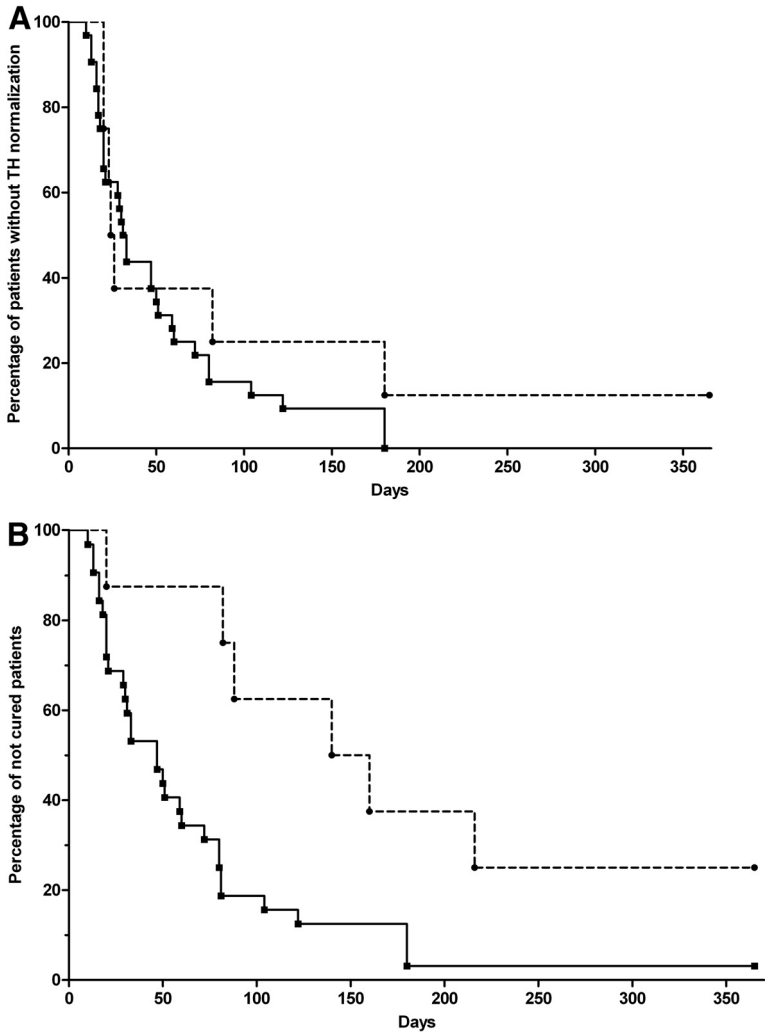

FIG. 1. A, Kaplan-Meier estimates of the proportion of patients not achieving first restoration of serum thyroid hormone concentrations (TH). AMIO-ON group patients (*dotted line*) and AMIO-OFF group patients (*continuous line*) were treated with prednisone. The normalization time was similar in the two groups (log rank, $P = 0.326$); the proportion of nonnormalized patients did not significantly differ in the two groups ($P = 0.200$). B, Kaplan-Meier estimates of the final nonhealing rate. The proportion of patients remaining thyrotoxic in the two groups was compared at the final follow-up. The AMIO-ON group (*dotted line*) and the AMIO-OFF group (*continuous line*) are shown. Euthyroidism restoration was delayed in AMIO-ON patients (log rank, $P = 0.011$); the final nonhealing rate was higher in the AMIO-ON group (25%) than in the AMIO-OFF group (3%), although not reaching a significant difference ($P = 0.096$), probably owing to the small sample size.

model was also used to evaluate whether additional covariates had an effect on the global cure time. A multivariate analysis was performed to compare the global cure time in the two groups; adjusting for the covariates resulted in significance at the univariate analysis.

A value of two-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 13.0 software (IBM, Milan, Italy).

Results

As expected, among the 40 patients included in the study, there was a predominance of men (87.5%). All 40 patients had, in addition to undetectable serum TSH, increased serum FT3 and FT4 concentrations (Table 2). No patient had detectable serum TgAb, TPOAb, or TRAb. Mean thyroidal 3- and 24-h RAIU value was 1.3 ± 0.8 and 0.8 ± 0.4%, respectively (≤5% in all cases). Mean thyroid volume was normal, but 16 patients (40%) had a small goiter with small nodule(s) (≤1 cm) or without nodules at conventional thyroid ultrasonography, equally distributed in the two study groups.

The clinical and biochemical features of the study groups at baseline are shown in Table 2. The two groups of patients were homogeneous and did not differ as to serum thyroid hormone concentrations, estimated (and normalized) thyroid volume, 3- and 24-h RAIU, cumulative dose of amiodarone, and duration of amiodarone treatment (Table 2). Only UIE values were higher in the AMIO-ON than in the AMIO-OFF group ($P = 0.020$), reflecting amiodarone therapy continuation.

The nonhealing curves of the AMIO-ON and the AMIO-OFF patients are shown in Fig. 1. The first normalization of serum thyroid hormone occurred after 24 and 31 d (median time) in the AMIO-ON patients and AMIO-OFF patients, respectively, without significant differences between the two groups (log rank, $P = 0.326$); serum thyroid hormone did not normalize in one AMIO-ON patient during the study period (Fig. 1A).

However, five of 7 patients in the AMIO-ON group (71.4%) and three of 32 patients in the AMIO-OFF group (9.4%) had recurrent thyrotoxicosis after the first normalization of thyroid hormone during glucocorticoid therapy ($P = 0.002$), requiring a second course of prednisone.

The final nonhealing rate was higher in the AMIO-ON group (25%) than in the AMIO-OFF group (3%), although not reaching a statistical difference ($P = 0.096$), likely due to the small sample size. However, in the AMIO-ON patients, the median cure time was significantly longer than that in AMIO-OFF patients [140 d; 95% confidence interval (CI) 40–240 and 47 d; 95% CI 26–68 d, respectively; log rank, $P = 0.011$] (Fig. 1B).

Results from the univariate and multivariate analyses by the Cox model are reported in Table 3. Variables significantly associated with the healing time were amiodarone ON/OFF ($P = 0.008$) and normalized thyroid volume (NTV) ($P = 0.007$). The significant negative

TABLE 3. Factors associated with delayed response to glucocorticoid therapy at Cox regression

Variables	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Amio-ON/OFF	0.33	0.12–0.77	0.008	0.33	0.12–0.75	0.007
Age (yr)	1.00	0.98–1.03	0.528			
BMI	1.03	0.94–1.14	0.434			
FT4 (pg/ml)	0.98	0.95–1.01	0.330			
FT3 (pg/ml)	0.96	0.90–1.02	0.269			
Third h RAIU (%)	0.75	0.41–1.17	0.239			
24th h RAIU (%)	0.78	0.19–2.30	0.688			
NTV (ml/m^2)	0.83	0.72–0.95	0.007	0.82	0.70–0.94	0.006
Thyroglobulin (ng/ml)	1.00	0.99–1.00	0.749			
Duration of amiodarone treatment (months)	1.00	0.99–1.02	0.250			
Cumulative dose of amiodarone (g)	1.00	0.99–1.00	0.671			
UIE (μg/liter)	1.00	0.99–1.00	0.390			

Factors associated with the probability of cure were evaluated using univariate and multivariate analysis by Cox regression. Treatment with amiodarone and NTV was associated with a longer cure time. BMI, Body mass index; HR, hazard risk.

relationship between Amio-ON, NTV, and the healing time was confirmed also by the multivariate analysis (Table 3).

Two patients in the AMIO-ON group underwent uneventful total thyroidectomy for the deterioration of heart conditions after the recurrence of thyrotoxicosis or for persistent thyrotoxicosis at the end of the follow-up period. Overall, three of 40 patients (7.5%) developed permanent or persistent hypothyroidism after restoration of euthyroidism with prednisone, requiring L-T_4 replacement therapy. Development of hypothyroidism was not related to a rapid restoration of normal TSH concentrations during glucocorticoid therapy; in fact, all three of those patients had thyrotoxicosis recurrence.

Discussion

Type 2 is by far the most prevalent form of AIT (2) and is characterized by serum thyroid hormone excess without thyroid hyperfunction (1, 3–5). This drug-induced destructive thyroiditis is treated, usually successfully, with glucocorticoids (1, 8). Response to glucocorticoid therapy may, however, be delayed in patients with marked thyrotoxicosis, reflecting severe thyroid damage (13). Type 2 AIT may spontaneously remit (15), but it may take several months to more than 1 yr for a stable restoration of euthyroidism (19). Indeed, a rapid correction of thyrotoxicosis is crucial in AIT patients because this condition represents a predictor of an adverse cardiovascular outcome (14). Amiodarone withdrawal is not always feasible owing to the underlying cardiac disease. Whether continuing amiodarone therapy may affect the cure rate and cure time in type 2 AIT patients treated with glucocorticoids is presently uncertain. Ideally, because amiodarone (and/or iodine) is the cause of thyroid damage and related thyrotoxicosis, its withdrawal should be beneficial. On the other hand, due to the long half-life of the drug (4), amiodarone discontinuation might prove useless, at least in the short run. A few small studies suggested that continuing amiodarone administration does not reduce the cure rate of AIT patients receiving either thionamides, glucocorticoids, or a combination of the two treatments (15, 16).

We carefully selected the patients enrolled in the present study to avoid differences in the predicted time needed to restore euthyroidism (13), thus making comparison between effectiveness of glucocorticoids in patients continuing or discontinuing amiodarone as reliable as possible.

Our results indicate that continuation of amiodarone does not significantly affect the first normalization of thyroid hormone in type 2 AIT patients treated with glucocorticoids. As a matter of fact, the normalization rate was very similar in patients continuing or discontinuing the drug after prednisone treatment was instituted. However, the final cure time was significantly longer, and the final cure rate was lower in the AMIO-ON patients, although not reaching a statistical significance likely due to the small sample size. The observation that AMIO-ON patients achieved euthyroidism later than AMIO-OFF patients argues against the idea that continuing amiodarone therapy is devoid of any effect on the therapeutic outcome. This concept is reinforced by the observation that the recurrence rate of thyrotoxicosis was significantly more frequent in AIT patients continuing amiodarone. It is tempting to speculate that continuing amiodarone perpetuates cytotoxic damage of the follicular cells notwithstanding glucocorticoids; the higher UIE levels found in the AMIO-ON group are in keeping with the higher amiodarone and its

metabolite concentrations likely present in those patients, thus supporting the pathogenic mechanisms of thyrotoxicosis recurrence; however, it cannot be completely excluded that iodine itself may have a direct role in the amiodarone-driven thyroid cytotoxicity, although iodine bound to the drug appears to be more likely (3). It is worth of noting that most patients in the AMIO-ON group had more frequently severe cardiac diseases than those in the AMIO-OFF group; whether this aspect may reflect intrinsic differences between groups potentially influencing therapy response is currently unknown.

Restoration of euthyroidism was delayed in most AMIO-ON patients compared with AMIO-OFF patients. Although no death occurred in the two groups at the end of follow-up, persisting thyrotoxicosis worsened cardiac function in an AMIO-ON patient, who experienced sustained ventricular tachycardia, requiring hospitalization and eventually total thyroidectomy. Likewise, an additional patient of the AMIO-ON group was finally treated with total thyroidectomy for persisting thyrotoxicosis after more than 1 yr. Factors associated with failure to restore euthyroidism were continuation of amiodarone therapy and severity of thyroid damage. A practical suggestion deriving from these results is that glucocorticoids should likely cautiously be tapered and withdrawn.

In conclusion, amiodarone continuation in type 2 AIT patients is associated with a longer cure time and delayed restoration of euthyroidism. If cardiac conditions are stable and euthyroidism is expected to be restored in a short time (likely $\leq$ 40 d), amiodarone can be safely discontinued and eventually reinstituted after euthyroidism restoration; if cardiac conditions are unstable and require amiodarone continuation, the drug should not be necessarily withdrawn. In the latter situation, a balance between longer exposure of the heart to thyroid hormone excess and a prompt control of thyrotoxicosis with total thyroidectomy should be considered (20–22).

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