The role of antithyroglobulin, antiperoxidase and anti-TSH receptor autoantibodies in amiodarone-induced thyrotoxicosis and amiodarone-induced hypothyroidism (A two-center study)

O R I G I N A L   A R T I C L E

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Abstract

OBJECTIVE: It has been reported that patients experiencing side effects of amiodarone (AM) therapy, such as amiodarone-induced thyrotoxocosis (AIT) or amiodarone-induced hypothyroidism (AIH), have changes in serum concentrations of anti-TSH receptor (TSHR), antithyroglobulin (Tg), and antiperoxidase (TPO) autoantibodies (Abs). The purpose of our study was to identify and analyze the changes in levels of listed antibodies in patients with several thyroid disorders.
METHODS: 280 patients from two centers in Poland were included. Titers of TSHR-Abs, TPO-Abs and Tg-Abs were analyzed retrospectively in the following groups of patients: A – euthyroid patients with a history of hyperthyroidism prior to re-administration of AM; B – patients with AIT who discontinued the AM therapy; C – patients with AIT chronically treated with AM; D – hypothyroid patients.
RESULTS: Serum Tg-Abs were not elevated in any of the studied groups. However, there were significant differences between A and B and also D and other groups ($p<0.05$). TPO-Abs titers were not elevated in most cases, there were no significant

differences between groups. The serum titers of TSHR-Abs were not elevated in any group. We found statistically significant differences between B and D, C and other groups (*p*<0.05).

CONCLUSIONS: Regardless of the statistically significant differences observed for Tg-Abs and TSHR-Abs levels, this observation have a limited clinical applicability. In almost all cases we observed normal to slightly increased titers of TPO-Abs, Tg-Abs, TSHR-Abs. Discontinuation or continuation of AM therapy had no influence on autoantibody titers. Furthermore, we found it impossible to differentiate between the type I and II of AIT based on autoantibody titers.

Abbreviations:

AAD	- antiarrhytmic drug
AF	- atrial fibrillation;
AIH	- amiodarone-induced hypothyroidism;
AIT	- amiodarone-induced thyrotoxicosis;
AM	- amiodarone;
IFN-α	- Interferon-α
RAIU	- radioiodine uptake;
Tg-Abs	- thyroglobulin autoantibodies
TH	- thyroid hormones;
TPO-Abs	- thyroperoxidase autoantibodies
TSHR-Abs	- autoantibodies to the thyrotropin receptor

INTRODUCTION

Amiodarone (AM) remains the most effective antiarrhytmic drug (AAD), particularly in the treatment of various chronic heart conditions (Singh *et al.* 1995, Mason *et al.* 1983). It is used in the primary prevention of atrial fibrillation (AF) or in the conversion of AF into sinus rhythm (Conolly 1999). AM is also used in treatment of ventricular tachyarrhythmias, especially in the prevention of sudden cardiac death (Reiffel *et al.* 1994). Unfortunately, AM therapy is associated with many side effects including severe toxicity of the lungs, liver, nerves, skin, and thyroid (Fogoros *et al.* 1983; Greene *et al.* 1983; Morady *et al.* 1983; Winkle *et al.* 1985; Czarnywojtek *et al.* 2013b).

The pathogenesis of the AM's effect on the thyroid is not entirely clear (Bartalena *et al.* 1996; Martino *et al.* 2001; Bogazzi *et al.* 2010). It may induce both hypothyroidism (AIH) and hyperthyroidism (AIT). In contrast to AIH, AIT constitutes great problem, even for experienced endocrinologists and nuclear medicine specialists. Due to amiodarone's long half-life it accumulates in tissues (Kurt *et al.* 2008; Han & Williams 2009). This means that hyperthyroidism may develop during AM therapy or many months after its withdrawal (Martino *et al.* 2001).

AIT is often classified into two different types. Type I AIT occurs in patients with underlying thyroid pathology like Graves' disease. In these patients the addition of a large amount of iodine from AM therapy leads to accelerated thyroid hormone synthesis – this is known as the Jod-Basedow phenomenon. In contrast, type II AIT is due to the direct toxic effect of AM and its metabolite (benzofuran) and it leads to destructive inflammation of the thyroid. In these patients, subacute thyroiditis results in excess release of fT3 and fT4 and subsequent severe hyperthyroidism. Type II AIT develops in people with a normal thyroid, often in areas rich in iodine (Martino *et al.* 2001). Clinically, it is very difficult to separate the two types of AIT (Bartalena *et al.* 2002; Piga *et al.* 2008; Bogazzi *et al.* 2010). Bedside radioiodine uptake (RAIU) (Martino *et al.* 2001), thyroid [99mTc]2-methoxy-isobutyl-isonitrile (MIBI) scintigraphy (Piga *et al.* 2008), IL-6 (usually elevated in type II AIT) (Martino *et al.* 1986; Bartalena *et al.* 1994; Martino *et al.* 2001), IL-13 (Bogazzi *et al.* 2012) and C-reactive protein (Pearce *et al.* 2003; Czarnywojtek *et al.* 2014) are believed to play a helpful role in facilitating the division of AIT type I and II. Moreover, it has been suggested that thyroid autoantibodies, which are found in the serum of some of patients undergoing AM therapy (Foresti *et al.* 1985; Monteiro *et al.* 1986; Martino *et al.* 2001), can be used to make this distinction: TSHR-Abs are thought to be associated with type I AIT, while TPO-Abs and Tg-Abs are thought to play a role in type II AIT. Therefore, in this study we examined the changes of the autoantibody titers in patients with AIT in an attempt to explore what role they have in the pathogenesis of amiodarone-induced thyroid dysfunction. Based on our results, we were not able to make a distinction between the two different types of AIT.

MATERIALS AND METHODS

The study consisted of 280 patients that were diagnosed in the Department of Endocrinology, Metabolism and Internal Medicine (217 patients) in Poznan, and in the Department of Nuclear Medicine (63 patients) in Warsaw, Poland between January 2003 and December 2014. TPO-Abs, Tg-Abs, TSHR-Abs were analyzed retrospectively, and compared in euthyroid, hyperthyroid (AIT), and hypothyroid (AIH) patients. Additionally, TSH and thyroid hormones (TH) were examined.

Patients

Initially, a retrospective analysis of the medical records was performed. There were 280 patients (225 males and 55 females, with a male: female ratio of 9.7:1) with ages ranging from 36 to 92 years (median age 67). The patients were divided into four groups:

- Group A: Euthyroid patients with a history of hyperthyroidism prior to the administration of AM (patients planned to have reintroduced AM as a lifesaving drug)
- Group B: Hyperthyroid patients (AIT) with normal radioiodine uptake [RAIU (+)], a half-year after discontinuation of AM.
- Group C: Hyperthyroid patients (AIT) with extremely reduced radioiodine uptake [RAIU (–)], chronically taking AM.
- Group D: Hypothyroid patients who had AM withdrawn after about 3 months of the therapy

The study design and procedures were approved by the Poznan University of Medical Sciences Medical Ethics Committee. All participants provided written consent.

Diagnosis of AIT and AIH

AIT was defined by the following criteria: increased fT4, fT3, and suppressed TSH levels that occurred during therapy or within two years after the AM withdrawal, and a negative titer of circulating thyroid autoantibodies (Tg-Ab, TPO-Ab, TSHR-Abs) (Han *et al.* 2009). AIH was defined by low levels of T3 or free T3, by age, and by an elevated TSH level after AM therapy (Connolly 1999).

Assays

Hormonal assessment of serum TSH (normal range: 0.27–4.2 μIU/mL), free thyroxine (fT4, normal range: 11.5–21.5 pmol/L) and triiodothyronine (fT3, norm range: 3.9–6.8 pmol/L)] was performed using a Hitachi Cobas e601 chemiluminescent analyzer (Roche Diagnostics, Basel, Switzerland). The TSH concentration was measured with a third-generation assay (sensitivity: 0.005 μIU/mL). The concentration of autoantibodies was assessed by the radioimmunological method using second-generation antibodies (RIA-2 Dynotest TRAK human, BRAHMS Diagnostic GmbH, Berlin, Germany). Normal ranges were defined according to the laboratory and kits they used. The ranges were as follows: TSHR-Abs <2 IU/L, Tg-Abs <115 IU/mL, TPO-Abs <35 IU/mL, free T4: 11.5–21.5 pmol/L, free T3: 3.9–6.8 pmol/L, and TSH: 0.27–4.2 μIU/mL.

Statistical analysis

The collected data were analyzed using the Statistica 10 from StatSoft (SSS), version 10.0 (Krakow, Poland). Descriptive data were presented as mean and standard deviation (SD). Due to the normal distribution, differences between quantitative data were evaluated by using ANOVA (Kruskal-Wallis test). In order to verify differences that existed amongst groups, a multiple comparisons Dunn test was performed. A *p*-value below 0.05 was considered statistically significant.

RESULTS

In group A (mean age: 50±19 years) the average dose of AM previously administered was from 150 to 900 mg/day. The median time of the withdrawal of the drug ranged from ½ to 3 years. In this group, AM was to be reintroduced in the case of life-threatening tachyarrhythmias. In group B (mean age: 71.5±11.9 years), the time of discontinuation of AM ranged from 6 to 27 months (median 11.2 months). The patients from this group were classified as having type I AIT due to RAIU (+). Patients from group C (mean age: 64.2±13.1 years, chronically taking AM), with RAIU (−), were classified to type II AIT. The daily dose of AM was 200 mg and the median time of therapy was 37 months (from 5 to 76

months). In group D – patients with AIH – (mean age: 65.1±16.6 years), the median time of the AM discontinuation was 17.5 months, ranging from 4 to 37 months.

Serum TSH, fT4 and fT3 concentrations are presented in Table 1. The highest concentrations of fT4 (32.3±8.0 pmol/L) and fT3 (12.1±11.5 pmol/L) were found in AIT patients with extremely reduced RAIU (−) chronically taking AM (group C). The lowest fT4 (10.5±1.9 pmol/L) and fT3 (3.7±0.6 pmol/L) were observed in hypothyroid patients (group D). The level of TSH was the lowest in group C (0.03±0.04 μIU/mL) and extremely high in the case of group D (9.2±3.9 μIU/mL). There were no significant differences regarding measured TSH, fT4 and fT3 in hyperthyroid groups B and C.

The titers of serum TSHR-Abs were not elevated in any of the studied groups. The mean values were: 0.5±0.2 (group A), 0.7±0.5 (group B), 1.0±0.7 (group C), and 0.4±0.3 IU/L (group D). We found statistically sig-

Tab. 1. Clinical manifestations and laboratory findings of study patients with AIT and AIH.

Variable	Group A	Group B	Group C	Group D
Number	82	98	78	22
Male:female ratio	1:4.4	1:3	1:6.8	1:2.6
Age (yr)	50±19	71.5±11.9	64.2±13.1	65.1±16.6
TSH (μIU/mL)	0.3±0.2	0.01±0.03	0.03±0.04	9.2±3.9
fT4 (pmol/L)	18.5±2.2	27.5±7.9	32.3±8.0	10.5±1.9
fT3 (pmol/L)	5.4±0.8	10.3±4.1	12.1±11.5	3.7±0.6
RAIU	25.4±12.8	16.2±24.7	1.9±0.4	11.3±4.9

Values are presented as mean ± standard deviation.
Reference values in our laboratory are as follows: fT4, 11.5–21.5 pmol/L; fT3, 3.9–6.8 pmol/L; TSH, 0.27–4.2 IU/L.
Abbreviations: TSH – thyroid-stimulating hormone, fT3 – free thriiodothyronine, fT4 – free thyroxine, RAIU – radioiodine uptake.
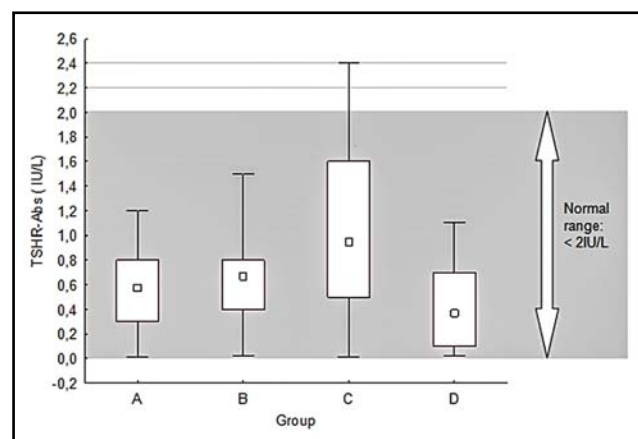
Fig. 1. Distributions of TSH receptor autoantibodies (TSHR-Abs) titer in all studied groups. Group A – euthyroid patients, group B – hyperthyroid patients with normal RAIU(+) (radioiodine uptake) as AIT type I, group C – hyperthyroid patients with extremely reduced RAIU(−) as AIT type II, and group D – hypothyroid patients (AIH, group D). Data are presented as means ± standard deviation.

nificant differences between groups: A and C (*p*=0.001), B and C (*p*=0.02), B and D (*p*=0.04), C and D (*P* = 0.02). Further details of these results are shown in Figure 1.

The titers of Tg-Abs were within the normal range or decreased in most cases. The levels of the mean serum Tg-Abs were 58.7±36.8, 40.7±26.9, 48.6±27.3 and 20.8±8.3 IU/ml, in groups A–D respectively. We found statistically significant differences between groups A and B (*p*=0.001), A and D (*p*<0.0001), B and D (*p*=0.003), C and D (*p*<0.0001). Results are shown in Figure 2.

In most cases, serum TPO-Abs titers were not elevated in any of the studied groups. The mean serum values of TPO-Abs were: 27.6±11.5 (group A), 25.0±14.3 (group B), 28.4±13.3 (group C), and 23.2±12.4 IU/mL (group D). The changes did not differ (Kruskal-Wallis

Fig. 2. The titer of antithyroglobulin autoantibody (Tg-Abs) in serum in all studied groups. Group A – euthyroid patients, group B – hyperthyroid patients with normal RAIU(+) (radioiodine uptake) as AIT type I, group C – hyperthyroid patients with extremely reduced RAIU(–) as AIT type II, and group D – hypothyroid patients (AIH, group D). Data are presented as means ± standard deviation.

Fig. 3. The level of thyroperoxidase autoantibodies (TPO-Abs) titer in all studied groups. Group A – euthyroid patients, group B – hyperthyroid patients with normal RAIU(+) (radioiodine uptake) as AIT type I, group C – hyperthyroid patients with extremely reduced RAIU(–) as AIT type II, and group D – hypothyroid patients (AIH, group D). Data are presented as means ± standard deviation.

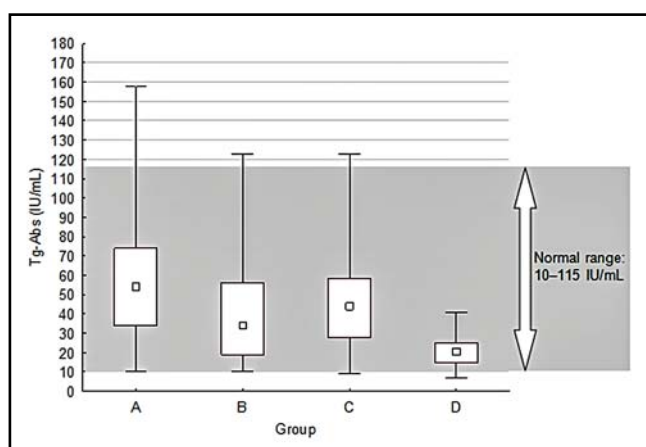test) between examined patients. Results are shown in Figure 3.

DISCUSSION

Thyroid autoantibodies (TPO-Abs, Tg-Abs, TSHR-Abs) play a crucial role in the development and differentiation of Hashimoto's and Graves' Diseases. For example, it is likely that autoimmunity against TSHR is what initiates the immune response in Graves' ophthalmopathy (Wiersinga 2011). On the other hand, the role of autoimmunity and the significance of anti-thyroid autoantibodies in the pathogenesis of amiodarone-induced thyroid dysfunction (AIT and AIH), in patients without pre-existent thyroid diseases, are still unclear. It is highly probable that the abnormal activation of T lymphocytes contributes to the destruction of thyroid tissue caused by TPO-Abs and Tg-Abs (Foresti *et al.* 1985; Martino *et al.* 1986).

In this study we tried to identify changes in TPO-Abs, Tg-Abs, and TSHR-Abs titers in all patients that were observed. Out of the 280 studied patients, in 258 patients with AIT (groups A, B, and C) and 22 with AIH (group D), the serum titers of thyroid Abs were not elevated – for the most part they fell in the normal range. Even though we found statistically significant differences in TSHR-Abs and Tg-Abs titers, they had no clinical implications because most titer values were in the normal range.
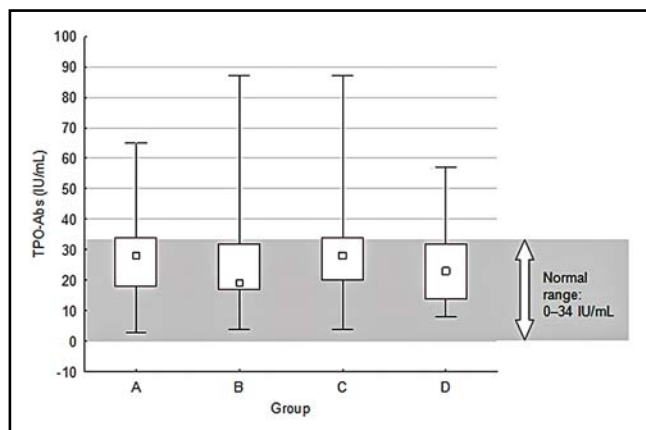
The fact that antibody titers in AIT and AIH were shown to be negative in our pilot study is significant because the existing literature on the topic is relatively scarce. Our data suggests that antithyroid Abs are of relatively minor importance in patients on AM therapy – both during the AM treatment and after its withdrawal. This begs the question: to what degree are autoantibodies instrumental in the pathogenesis of AIT and AIH? Are they useful in differentiating between type I (a form of Jod Basedow) and type II (destructive thyroiditis) AIT (Bartalena *et al.* 2004)?

In earlier observations, thyroid autoantibodies were sometimes claimed to be present in type I AIT. According to Martino E *at al.* (Martino *et al.* 1986), circulating thyroid Abs could be found in all AM-induced hyperthyroid patients (particularly in toxic diffuse goiter), while they were rare in toxic multinodular goiter. Monteiro E *et al.* (Monteiro *et al.* 1986) observed serum TPO-Abs titer after 30 days of the therapy of AM in 55% of patients. In contrast, levels of Abs were usually absent in AIT type II (Foresti *et al.* 1985; Martino *et al.* 1986). In this way, Abs levels have been used to differentiate between the types of AIT. Our study challenges these observations. It is our opinion that thyroid Abs do not play a role in the distinction of AIT types.

As noted, in our current study, Ab titers in AIT and in AIH were within normal range. This is in contrast to our previous studies of interferon-α-induced hyperthyroidism (IIH), where the antibody titer was

significantly higher. In terms of interferon-α therapy, we can clearly differentiate two types of hyperthyroidism. Type I is related to Graves' disease (high titer of TSHR-Abs) and Type II is related to thyroid destruction (Hashitoxicosis), where titers of TSHR-Abs are always in the normal range. Hence, we can conclude that in contrast to AM, INF-α can cause Graves' disease or Hashitoxicosis, and there is no clinical problem with differentiation into two types (Czarnywojtek *et al.* 2013). However, in the case of AIT, differentiation is a great challenge even for an experienced endocrinologist or nuclear medicine specialist. In clinical practice most patients have mixed forms of AIT and, according to Han TS (Han *et al.* 2009) as well as our own observations (Czarnywojtek *et al.* 2014b), it is often impossible to distinguish type I and type II disease.

Limitations of the study were as follows:

The study group was very heterogeneous. On one hand, a large group of patients helped give a more precise estimation of the role of thyroid Abs in the development of AIT. On the other hand the diversity amongst patients studied may confuse the reader.

Statistical calculations of autoantibody titers were made based on a nonparametric test due to normal distribution, because variables of Abs (Tg-Abs, TPO-Abs, and TSH-R Abs) are measured on an interval scale, so the values were presented as mean and SD.

The outcome of our study can be summarized as follows: discontinuation or continuation of AM therapy has no influence on the titer of serum thyroid autoantibodies. The statistically significant differences that were observed were not clinically relevant. The role of autoimmunity and the significance of anti-thyroid autoantibodies in the pathogenesis of amiodarone-induced thyroid dysfunction in patients with pre-existent thyroid diseases remains unclear. Furthermore, we concluded that it is not possible to differentiate between the classifications of AIT (types I and II) based on their antibody titers.

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