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ORIGINAL ARTICLE

Antithyroid drugs in Graves' hyperthyroidism: differences between "block and replace" and "titration" regimes in frequency of euthyroidism and Graves' orbitopathy during treatment

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Abstract

Purpose Whereas antithyroid drugs (ATD) are the preferred treatment modality for Graves' hyperthyroidism (GH), there is still controversy about the optimal regimen for delivering ATD.

To evaluate whether 'Block and Replace' (B + R) and 'Titration' (T) regimes are equivalent in terms of frequency of euthyroidism and Graves' Orbitopathy (GO) during ATD therapy.

Methods A prospective multicentre observational cohort study of 344 patients with GH but no GO at baseline. Patients were treated with ATD for 18 months according to B + R or T regimen in line with their institution's policy.

Results Baseline characteristics were similar in both groups. In the treatment period between 6 and 18 months thyrotropin (TSH) slightly increased in both groups, but TSH was on average 0.59 mU/L (95% CI 0.27–0.85) lower in the B + R group at all time points ($p = 0.026$). Serum free thyroxine (FT4) remained stable during the same interval, with a tendency to higher values in the B + R group. The point-prevalence of euthyroidism (TSH and FT4 within their reference ranges) increased with longer duration of ATD in both groups; it was always higher in the T group than in the B + R group: 48 and 24%, respectively, at 6 months, 81 and 58% at 12 months, and 87 and 63% at 18 months ($p < 0.002$). There were no significant differences between the B + R and T regimens with respect to the fall in thyrotropin binding inhibiting immunoglobulins (TBII) or thyroid peroxidase antibodies (TPO-Ab). GO developed in 15.9% of all patients: 9.1 and 17.8% in B + R group and T group, respectively, ($p = 0.096$). GO was mild in 13% and moderate-to-severe in 2%.

Conclusion The prevalence of biochemical euthyroidism during treatment with antithyroid drugs is higher during T compared to B + R regimen. De novo development of GO did not differ significantly between the two regimens, although it tended to be higher in the T group. Whether one regimen is clinically more advantageous than the other remains unclear.

Keywords Graves' disease treatment · Graves' orbitopathy · Hyperthyroidism · Antithyroid drugs

Introduction

Antithyroid drugs (ATD) are nowadays the preferred treatment for the first episode of Graves' hyperthyroidism (GH). In Europe, Latin America and Japan physicians have always preferred ATD over thyroid surgery or radioactive iodine (RAI) in up to 85–90% of uncomplicated cases [1, 2]. In contrast, most patients in the USA used to be treated with RAI. However, recent surveys show a decline in the use of RAI and increased use of ATD in the USA: in 1991, 2011 and 2014 RAI was preferred by 69, 59 and 35% respectively, whereas ATD was preferred by 31, 41 and 58% of USA respondents [1–3].

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Current guidelines recommend methimazole (MMI) in non-pregnant patients who choose ATD therapy for GH [4, 5], although the recent addition of acute pancreatitis as a serious, albeit rare, side effect to MMI has opened the possibility of a change in this balance of ATD recommendation [6, 7]. ATD can be administered according to either the 'Block and Replace' (B + R) regimen where a fixed high-dose of ATD is combined with levothyroxine (LT4) with subsequent changes in the dose of LT4 as necessary according to results of thyroid function tests or to the 'Titration' (T) regimen where the ATD dose is titrated against the results of thyroid function tests. There has never been a randomized clinical trial comparing head-to-head the two regimes. A Cochrane Database Systematic Review concludes that neither regimen is superior in terms of higher remission and lower recurrence rates after a course of ATD. Relapse rates were similar in both groups (51% in B + R and 54% in T), but skin rashes (10% vs. 6%) and withdrawal due to side effects (16% vs. 9%) were significantly more frequent in the B + R group [8].

It is claimed that B + R is associated with more stable thyroid function and that patients treated with B + R may require fewer thyroid function tests and clinic visits [9]. This has been investigated in a retrospective observational study in the UK [10]. The annual number of thyroid function tests and the annual number of hospital clinic visits were lower in the B + R group than the titration group. The number of abnormal thyroid function tests per year was similar in the two groups. Thus, there was little evidence that patients under B + R have more stable thyroid function. The higher rate of side effects in the B + R group has led guidelines to favour the T regimen, albeit not recommending against the B + R regimen [4, 5]. The use of both regimes is common in clinical practice. For example, a third of endocrinologists in the UK use B + R, whilst the remainder favour titration [11]. Recently we published the results of a multicentre prospective observational study in patients with newly diagnosed GH, scheduled to be treated with a course of ATD, and aiming to predict the development of Graves' orbitopathy (GO) from baseline data [12]. Participating centres administered ATD according to either the B + R or the T regimen, in accordance with their institution's established policy. It allowed us to compare both regimens with regard to the maintenance of a stable thyroid function and the development of GO.

Patients and methods

Patients

Patients were recruited from ten participating centres of the European Group on Graves' Orbitopathy (EUGOGO) in the period May 2009–May 2014. Inclusion criteria were untreated GH, absence of overt GO and planned treatment with ATD for 18 months. Definition of GH was (1) decreased TSH, elevated FT4 and/or FT3 and (2) a diffuse thyroid gland (either by palpation or ultrasonography) and/or homogeneous thyroid uptake at scintigraphy. ATD could be administered according to either the T or the B + R regimen, in line with the standard policy of each participating centre. Exclusion criteria were (A) previous or planned treatment with 131-I or thyroidectomy, (B) presence of GO, defined as one or more of the following eye findings: (1) soft tissue changes (moderate or severe eyelid/conjunctival redness, moderate or severe eyelid/periorbital swelling) as depicted in the colour atlas [13]; (2) proptosis above the upper normal limit (Asians 18 mm, Caucasians 20 mm, blacks 22 mm); (3) diplopia (intermittent, inconstant or constant); (4) decreased visual acuity attributable to GO, (C) drugs interfering with the natural course of GO (e.g., glucocorticoids, cytokines, anticytokines, thiazolidinediones, selenium), (D) drugs interfering with thyroid function (e.g., amiodarone, lithium, iodine supplements), (E) drug or alcohol abuse, (F) lack of informed consent. Approval of institutional review boards or local ethical committees was not deemed necessary because the study protocol did not require additional procedures beyond those done in the delivery of usual care. Nevertheless, consent has been obtained from each patient after a thorough explanation of the purpose and nature of all procedures.

Three hundred and ninety-two patients were recruited. Eleven patients were subsequently excluded [nine opted for thyroidectomy (B + R 3, T 6) and one for 131-I (B + R), and one patient suffered a stroke (B + R)]. Another 33 patients were lost to follow-up (B + R 12, T 21), and no treatment modality data were recorded for four patients, leaving 344 patients for analysis. Of 344 patients 66 were treated using B + R and 278 using T regimen. Six centres used only T regimen and four centres used both T and B + R regimen.

Subclinical hypothyroidism was diagnosed when FT4 was normal reference laboratory range and but TSH above the upper reference range.

Subclinical hyperthyroidism was diagnosed when FT4 was within normal reference laboratory range and but TSH below the lower reference range. However, T3 has not been measured in all samples, so too small sample did not allow to analyse the presence of the T3-toxicosis.

Study protocol

This was a prospective cohort study. Eye changes were assessed as described previously [12]. ATD were commenced after blood sampling. Follow-up visits at 6, 12, and 18 months included blood sampling and reassessment of smoking behaviour and eye changes. Endpoints of the study were assessed after 18 months of ATD, or development of GO as defined under exclusion criterion two (GO was also

diagnosed if proptosis values had increased by more than 2 mm). Premature stops occurred when clinician and patient opted for 131I therapy or thyroidectomy based on a valid clinical reason, earlier than 18 months or in case of severe intercurrent illness.

Laboratory analyses

Investigation of thyroid function and thyroid antibodies were performed at each centre in the local laboratory. As different assays with different reference values were used, all obtained results were normalized by dividing obtained results by the upper normal limit of that assay, and then multiplied by the most common upper limit of the reference range [14]. Thyrotropin binding inhibiting immunoglobulins (TBII) was measured by second-generation assays [15]. Thyroid peroxidase antibodies (TPO-Ab) were measured by ELISA.

Statistical analysis

Normally distributed data are reported as mean ± SD, while data not normally distributed are reported as median with interquartile range (percentile 25/P25/ to percentile 75 / P75/). Categorical variables are recorded as numbers and percentage.

To assess relations between ATD regimen, time since the start of treatment, and centre with TSH, FT4, TBII or TPO-Ab mixed-effects regression was used. R and Ime4 software were used [16, 17]. ATD regimen and time since the start of treatment were entered as fixed effects, and random intercept and slope for a patient within the centre was used. There was no significant interaction between ATD regimen and time since the start of treatment in any of the models. Because of the wide variation of the data, logarithmic transformations for TSH, FT4, TBII and TPO were used.

To asses, the influence of ATD regimen, time and centre on achieving euthyroidism and Graves' orbitopathy, mixed-effects logistic regression was done. ATD regimen and time were entered as fixed effects, and random intercept and slope for a patient within the centre were used. There was no significant interaction between ATD regimen and time in any of the models.

Correction for multiple comparisons was done using Holm's method [18].

Results

Three hundred and forty-four patients were included; 66 (19%) were treated with the B + R regimen and 278 (81%) with the T regimen. Baseline characteristics of the two groups did not differ except for overrepresentation of non-Caucasians in the B + R group (Table 1). Laboratory data are given in Table 2. For analysis of changes in serum TSH and FT4, we did not include baseline concentrations (time zero) because TSH values were always low and FT4 high in the untreated stage of hyperthyroidism. TSH concentrations slightly increased in the period from 6 to 18 months, both in the B + R and in the T group. TSH values were significantly lower (by 0.59 mU/L; 95% CI 0.27–0.85) in the B + R group compared to the T group ($p = 0.026$) at each time point. FT4 concentrations were stable during the period from 6–18 months in both groups; FT4 values were not significantly different between the T and B + R groups ($p = 0.214$), although FT4 tended to be higher in the B + R group. There were differences between centres in TSH and FT4 changes. In some centres, at 6 months TSH was higher and FT4 lower than in other centres, and vice versa (intercept in Fig. 1). Also, TSH change during the 6–18 months period differed between centres (slope in Fig. 1). Usually, centres with higher serum TSH values at 6 months had a smaller slope of serum TSH change. These data imply differences in therapeutic approaches employed by different centres with some initially instituting more intensive ATD treatment than others.

All patients responded to ATD, especially during the first 6 months of the treatment. There were no non-responders in any of the groups.

Euthyroidism was defined as serum TSH and FT4 concentrations within their respective reference ranges. The prevalence of euthyroidism increased with duration of ATD in both groups; it was always higher in the T group than in the B + R group (Table 3). Odds ratio's for achieving euthyroidism were 5.25 (95% CI 2.38–12.65) for T vs. BR regimen, 9.27 (95% CI 5.49–16.51) for 12 months vs. 6 months, and 12.29 (95% CI 7.14–22.41) for 18 months vs. 6 months. A detailed analysis of thyroid status at 6, 12 and 18 months are provided in Table 4. At each time point, the number of euthyroid patients was 23% higher in patients from the T group compared to patients from the B + R group. This difference of 23% in the prevalence of euthyroidism is completely attributable to a 23% higher prevalence of (subclinical + overt) hyperthyroidism at 6 and 18 months in the B + R group, whereas at 12 months the 23% difference in euthyroidism is due to a higher prevalence of both (subclinical and overt) hypothyroidism and (subclinical and overt) hyperthyroidism (9.5 and 13.7% respectively) in the B + R group. Both TPO-Ab and TBII values were significantly reduced during treatment with ATD (p values for trend: TPO-Ab 0.011, TBII < 0.001). There were no differences between the B + R and T regimens with respect to the decrease in TBII or TPO-Ab concentration, although it seemed that TPO-Ab decreased during B + R regiment but not during T (Table 2).

During treatment with ATD for 18 months, GO developed in 15.9% of all patients, especially during the 1st year

Table 1 Baseline characteristics of 344 patients with Graves' hyperthyroidism according to block and replace (B + R) regimen or titration (T) regimen

	B + R ($N = 66$	Titration ($N = 278$)	T ($N = 344$)	p value
Sex				
Female	53 (80.3%)	231 (83.1%)	284 (82.6%)	0.591[a]
Male	13 (19.7%)	47 (16.9%)	60 (17.4%)	
Age (years)				
Mean (SD)	41.6 (14.5)	43.1 (12.8)	42.8 (13.1)	0.381[b]
Ethnicity				
Caucasian	48 (72.7%)	269 (96.8%)	317 (92.2%)	< 0.001[a]
Other	18 (27.3%)	9 (3.2%)	27 (7.8%)	
Family history of AITD				
No	33 (73.3%)	189 (80.8%)	222 (79.6%)	0.312[a]
Yes	12 (26.7%)	45 (19.2%)	57 (20.4%)	
Other AI disease in a patient				
No	59 (89.4%)	264 (95.3%)	323 (94.2%)	0.079[a]
Yes	7 (10.6%)	13 (4.7%)	20 (5.8%)	
Never/ex/current smokers				
Never smoker	36 (54.5%)	162 (58.3%)	198 (57.6%)	0.210[a]
Ex-smoker	13 (19.7%)	32 (11.5%)	45 (13.1%)	
Current smoker	17 (25.8%)	84 (30.2%)	101 (29.4%)	
Smoking (pack-years)				
Median (P25, P75)	8.8 (4.1, 22.1)	20.0 (9.5, 24.2)	15.0 (7.5, 24.0)	0.063[c]
Cigarettes per day				
Mean (SD)	9.9 (5.1)	13.2 (7.2)	12.6 (6.9)	0.094[b]
Duration of symptoms (months)				
Median (P25, P75)	3.0 (1.9, 6.0)	3.0 (1.5, 5.0)	3.0 (1.5, 5.6)	0.368[c]

[a]Fisher's exact test for count data

[b]Linear model ANOVA

[c]Kruskal–Wallis rank-sum test

Table 2 Thyroid function tests and thyroid antibodies at baseline and during treatment with antithyroid drugs for 18 months according to block and replace (B + R) regimen or titration (T) regimen in 344 (B + R $n = 66$ and T $n = 278$) patients with Graves' hyperthyroidism

Drug regimen	Time 0	Time 6	Time 12	Time 18	p
TSH mU/L	Reference values 0.4–4.0				$p_{(time)} = 0.109$* $p_{(treatment)} = 0.026$*
B + R	0.02 (0.01, 0.02)	0.30 (0.02, 1.25)	1.00 (0.39, 2.59)	1.14 (0.22, 2.07)	
T	0.00 (0.00, 0.02)	0.80 (0.09, 2.34)	1.54 (0.80, 2.64)	1.70 (0.99, 2.50)	
FT4 pmol/L	Reference values 10.3.4–24.5				$p_{(time)} = 0.265$* $p_{(treatment)} = 0.214$*
B + R	40.2 (29.8, 60.5)	16.6 (11.1, 19.6)	15.2 (12.3, 18.1)	17.1 (13.9, 20.4)	
T	35.6 (26.6, 49.2)	14.2 (12.1, 17.2)	14.3 (12.6, 16.8)	15.6 (13.5, 16.9)	
TPO-Ab kU/L	Reference values 0–34				$p_{(time)} < 0.001$ $p_{(treatment)} = 0.408$
B + R	265.5 (72.2, 600.0)	121.0 (12.0, 394.3)	71.5 (8.8, 149.4)	45.0 (9.5, 141.5)	
T	178.0 (44.8, 1342.5)	228.9 (33.4, 1230.8)	207.4 (28.3, 905.5)	179.0 (28.3, 1022.8)	
TBII U/L	Reference values 0–1.5				$p_{(time)} = 0.011$ $p_{(treatment)} = 0.693$
B + R	6.6 (3.3, 12.2)	2.0 (0.7, 6.0)	1.0 (0.5, 2.9)	0.8 (0.5, 2.8)	
T	6.9 (3.9, 13.9)	3.9 (1.6, 8.7)	2.4 (1.1, 6.3)	1.2 (0.6, 3.0)	

Data as median values with interquartile range between brackets

*Analysed period 6–18 months

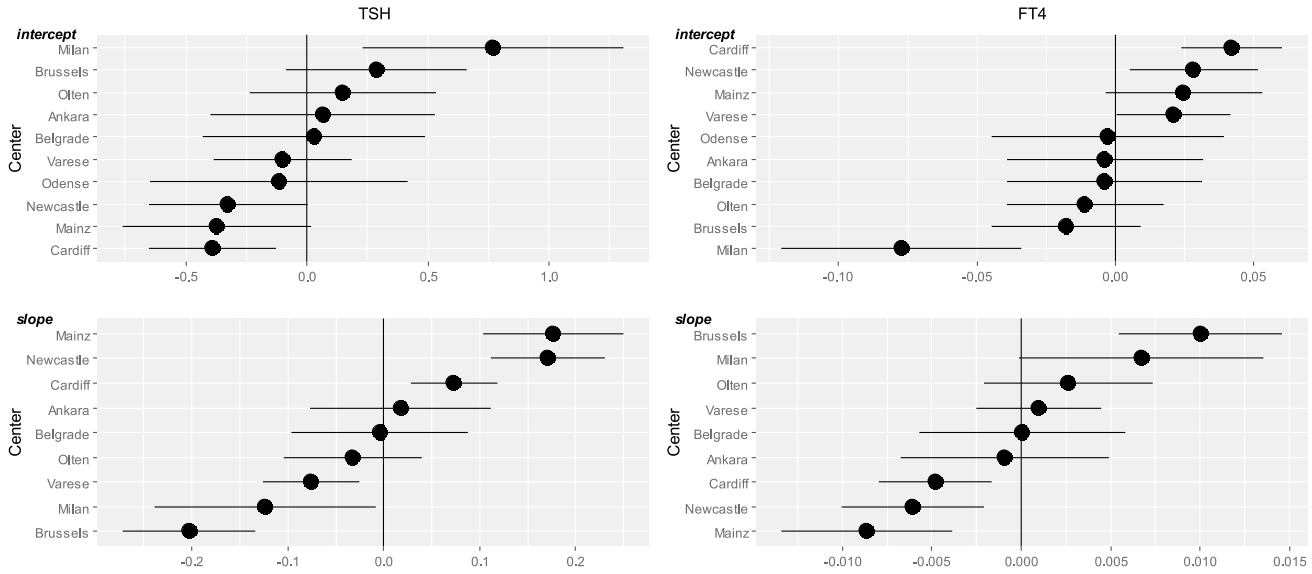

Fig. 1 Centre-specific changes in serum TSH and FT4 during treatment with ATD in the period between 6 and 18 months. Data are presented as the difference of centre specific intercept/slope from common (all centre) intercept/slope (±95% CI for difference)

Table 3 The proportion of euthyroid patients (defined as serum TSH and FT4 within their respective reference ranges) among 344 patients with Graves' hyperthyroidism treated with antithyroid drugs (ATD) according to block and replace (B + R) regimen or titration (T) regimen

Duration of treatment with antithyroid drugs (ATD)	B + R (n = 66) % euthyroid	T (n = 278) % euthyroid	p value*
0 months	0%	0%	
6 months	24.5%	47.8%	0.002
12 months	58.2%	81.4%	0.001
18 months	62.7%	85.6%	0.001

*corrected for multiple comparisons (Holm's method); time zero not included

of treatment (Table 5). GO was mild in 13% and moderate-to-severe in 2%. Although the proportion of patients developing GO was less in the B + R group (9.1%) compared to the T group (17.8%), the difference was not statistically significant ($p = 0.096$, Table 5).

No serious adverse effects were noted in our patient cohort. Other side effects were not reported. Three hundred and forty-four patients completed 18 months of the study. However, 33 patients were lost to follow-up (Total patients 344 + 33 = 377, B + R 12 patients, 15.4% of B + R patients, T 21 patients 7% of T patients, $p = 0.026$, odds ratio 2.4), significantly more in the B + R group.

Discussion

Between 6–18 months there was a slight increase in serum TSH which occurred independently of a regimen. The proportion of euthyroid patients (defined as TSH and FT4 values within their respective reference ranges) was higher in the T group than in the B + R group at each time point. This difference was remarkably similar at 6, 12 and 18 months, namely 23 percentage points. At 6 and 18 months, the difference was solely attributable to a higher frequency of (overt and subclinical) hyperthyroidism in the B + R group, whereas at 12 months the difference was due to a higher frequency of both (overt and subclinical) hypothyroidism and hyperthyroidism in the B + R group. The likely explanation for these observations is that in the B + R regimen, LT4 was added once the serum FT4 had become normal, usually 4–6 weeks after starting the ATD. It is well known that hypothyroid patients treated with LT4, require slightly higher serum FT4 values to reach normal TSH values [19]. If the same mechanism is at play in GH patients treated according to the B + R regimen, slightly higher serum FT4 concentrations could likely lead to a higher prevalence of suppressed TSH. In support of this explanation, serum TSH values were lower in the B + R group, in line with the trend of higher FT4 values in the same group. This was also true for the subgroup of patients who still had (subclinical or overt) hyperthyroidism at 6, 12 or 18 months after the start of ATD (Supplemental Table 1). Another likely explanation for higher FT4 levels in B + R is the transient peak in FT4 after ingestion of LT4, which does not apply to the T group. Also, identical thyroid function tests such as suppressed

Table 4 Thyroid state in 344 patients with Graves' hyperthyroidism during treatment with antithyroid drugs for 18 months according to block and replace (B + R) regimen or titration (T) regimen

Duration of treatment with antithyroid drugs	Thyroid function	B + R group (n = 66)	T group (n = 278)	p value (B + R vs. T)
6 months	Overt hypo	3.8%	4.8%	0.005
	Subclinical hypo	9.4%	8.3%	
	Euthyroid	24.5%	47.8%	
	Subclinical hyper	47.2%	34.3%	
	Overt hyper	15.1%	4.8%	
12 months	Overt hypo	3.6%	1.8%	0.003
	Subclinical hypo	12.7%	5.0%	
	Euthyroid	58.2%	81.4%	
	Subclinical hyper	18.2%	10.9%	
	Overt hyper	7.3%	0.9%	
18 months	Overt hypo	3.4%	2.3%	0.001
	Subclinical hypo	3.4%	3.7%	
	Euthyroid	62.7%	85.6%	
	Subclinical hyper	25.4%	7.4%	
	Overt hyper	5.1%	0.9%	

Table 5 The proportion of patients developing Graves' Orbitopathy (GO) in a population of 344 patients with Graves' hyperthyroidism treated for 18 months with antithyroid drugs according to block and replace (B + R) regimen or titration (T) regimen

Duration of treatment with antithyroid drugs (ATD)	Total group (n = 344) % GO	Block + replace group (n = 66) % GO	Titration group (n = 278) % G =	p value* (B + R vs. T)
0 months	0%	0%	0%	
6 months	7.6% (n = 26)	3.1% (n = 2)	8.6% (n = 24)	0.192/0.384
12 months	5.8% (n = 20)	1.6% (n = 1)	6.9% (n = 19)	0.090/0.360
18 months	2.6% (n = 9)	4.8% (n = 3)	2.3% (n = 6)	0.405/0.405
Total	15.9% (n = 55)	9.1% (n = 6)	17.8% (n = 49)	0.096/0.360

*Fisher's exact test, first p value uncorrected, second p value corrected for multiple comparisons (Holm's method)

TSH associated with slightly raised FT4 but normal FT3, may acceptable for B + R, while they are likely to trigger an increase in the dose of ATD in patients treated with T.

We did not notice a difference in side effect between the groups. However, a higher prevalence of patients lost to follow-up in the B + T group might be due to side effects, but we have no proof of that.

Inevitably, we conclude that euthyroidism during treatment with ATD is more prevalent with the T than with the B + R regimen. Consequently, should the B + R regimen be discarded, and the T regimen favoured in all cases? In our opinion, it is premature to abandon the B + R regimen altogether. Vaidya et al. have shown that the B + R regimen is associated with lower requirement for thyroid function testing and less hospital clinic visits per year [11]. Another advantage of the B + R regimen could be the assumed reduction of risk of developing GO. Yet, the present study gives no support to this claim, as the incidence of GO did not differ between the two regimens. However, although statistically not significant (most likely due to too small sample size), the frequency of GO was twice as high in the T group as in the B + R group. Given TSH receptor antibodies being positively related to the activity and severity of GO [20], the similar fall in TBII in both B + R and T would be in line with the lack of difference in the GO incidence between the regimes. Also, longer duration of hyperthyroidism is a prognostic factor for GO development, and patients treated with B + R regimen indeed had a longer duration of hyperthyroidism (Table 4) [12].

Euthyroidism is more prevalent during the T than during the B + R regimen and even occurs with a low ATD dose. Low dose treatment T regimen has minimal adverse effects, making it a viable long term treatment for patients who are not willing to accept other options [21].

Strengths of the present study include that it is prospective and based on a real-world everyday choice of the ATD regimen in various centres and countries, which suggest robustness in relation to the type of GH patients and geographic variation. Also, the strength of this study was the

thoroughness of the assessments for GO by the centres with a large experience in GO treatment.

Limitations include the relatively small number of the B + R patients, absence of documentation of side effects, absence of data on additional blood tests taken outside the time points 6, 12 and 18 months and frequency of dose adjustment in medication, and the absence of a complete set of serum FT3 data. Also, it is unclear from these data whether the differences in euthyroidism observed between the two regimens were related to the type of decision-making and advice administered by clinicians with regards to adjustment of medication, or the extent of adherence displayed by patients. The study is underpowered to detect an effect of the ATD regimen on the development of GO. Under optimal conditions with 1:1 allocation of patients, a sample size of 1042 subjects will be required to reach a power of 0.8. Our data show that wide variation exists between centres on choice of B + R or T regimens, which can lead to differences in the frequency of blood sampling in both regimens, when and how much LT4 is added in the B + R regimen, and when and to what extent the ATD dose is adjusted in the T regimen. Another limitation of this study is the lack of quality of life assessment and lack of pharmacoeconomic evaluation of regimens. Also, we did not assess the quality of life.

We conclude that the prevalence of biochemical euthyroidism during treatment with ATDs was higher during T compared to B + R regimen. De novo development of GO did not differ significantly between the two regimens, although it tended to be higher in the T group. Whether one regimen is clinically more advantageous than the other remains unclear, although it seems that T regimen has the advantage in the maintenance of euthyroidism. Our study highlights that randomised controlled trials focusing on the effects of ATD regimens on the development of GO are needed to address this important question.

Acknowledgements In memoriam George von Arx: On November 25, 2017, Dr. Georg von Arx, an outstanding physician,clinical researcher and tutor, passed away. He established the Joint Thyroid Eye Clinics inSwitzerland and shaped the multidisciplinary collaboration like no other.

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Data availability Because of the privacy protection laws data are not available.

Compliance with ethical standards

Conflict of interest Authors declare that there were no conflict or competing interests.

Ethical approval Approval of institutional review boards or local ethical committees was not deemed necessary because the study protocol did not require additional procedures beyond those done in the delivery of usual care. Decisions of the Ethical committee of the Academisch Medisch Centrum, Universiteit van Amsterdam and Ethical committee of the Clinical Centre of Serbia were obtained. Also, HRA-decision tool (https://www.hra-decisiontools.org.uk/ethics/) was used to confirm that ethical committee approval for UK was not required.

Informed consent Consent has been obtained from each patient after full explanation of the purpose and nature of all procedures.

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