Positive Impact of Long-Term Antithyroid Drug Treatment on the Outcome of Children with Graves' Disease: National Long-Term Cohort Study

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Context: Drug-based therapy is usually the initial treatment for Graves' disease (GD) hyperthyroidism in children, but there is some debate about treatment duration.

Objective: Our objective was to assess the effect of long-term carbimazole therapy on GD remission in children and its determinants.

Design and Setting: This was an observational prospective multicenter follow-up cohort study.

Participants: Participants included 154 children newly diagnosed with GD between 1997 and 2002. The intention was to treat patients with three consecutive courses of carbimazole, each lasting 2 yr. Definitive treatment was performed in cases of poor compliance with antithyroid drug (ATD) treatment, thyrotoxicosis relapse, or major adverse effects of ATD treatment.

Main Outcome Measure: The main outcome measure was remission for at least 18 months after the completion of each course of ATD treatment.

Results: The median duration of follow-up was 10.4 (9.0–12.1) yr. Overall estimated remission rates (95% confidence interval) 18 months after the withdrawal of ATD treatment increased with time and were 20 (13–26), 37 (29–45), 45 (35–54), and 49 (40–57)% after 4, 6, 8, and 10 yr follow-up, respectively. A multivariate competing risk model revealed an independent positive effect of less severe forms of hyperthyroidism at diagnosis [subhazard ratio of 1 for patients with free T_4 <35 pmol/liter *vs.* 0.4 (0.20–0.80) for free $T_4 \geq 35$ pmol/liter; $P = 0.01$] and of the presence of other autoimmune conditions [subhazard ratio of 2.23 (1.19–4.18); $P = 0.01$] on remission rate after medical treatment.

Conclusion: About half the patients achieved remission after carbimazole discontinuation, and there seems to be a plateau in the incidence of remission achieved after 8–10 yr ATD therapy. (***J Clin Endocrinol Metab* 97: 110–119, 2012**)

The optimal treatment of Graves' disease (GD) in childhood remains a matter of debate (1–5). Current treatment options include antithyroid drugs (ATD), subtotal or near-total thyroidectomy, and radioactive iodine (iodine-131). There is no specific cure for the disease, and each therapeutic option has associated complications (2, 3, 6, 7). Most patients are initially treated with ATD. However, it is difficult to achieve long-term compliance, and the rate of relapse is high in children, because remission is achieved in less than 30% of children after a first course of ATD for

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Abbreviations: ATD, Antithyroid drug; CI, confidence interval; FT_4, free T_4; GD, Graves' disease; SDS, SD score; SHR, subhazard ratio; TPOAb, thyroid peroxidase autoantibodies; TRAb, TSH receptor antibodies.

about 2 yr (8–14). Surgical removal of the thyroid gland and destruction of the gland by radioiodine treatment are therefore often used as alternatives. Indications for definitive treatment in children include relapse after an appropriate course of drug treatment, a lack of compliance on the part of the patient or the parents, and ATD toxicity. As in many rare diseases, there is currently no evidence-based strategy for the management of this disease in children, unlike in adults, in whom the disease is more frequent and remission rates are higher (15–17). GD treatment policy varies considerably within and between countries and depends on local traditions and resources, the age and preference of the patient, the size of the goiter, and the severity of the disease.

We have shown that a longer initial duration of euthyroid state with ATD is associated with a lower risk of relapse after a first course of ATD therapy (14). Severity factors for hyperthyroidism at presentation, defined as high serum concentrations of thyroid hormones and TSH receptor antibodies (TRAb), young age, and not being Caucasian were found to be independently and significantly associated with a higher probability of hyperthyroidism relapse. However, little is known about long-term outcome, because there have been few studies of the relationship between ATD treatment duration and remission rate or relapse risk in pediatric patients. The need to prescribe longer courses of treatment than in adult patients is widely accepted (18). In a retrospective analysis, Lippe *et al.* (19) demonstrated that remission rates in 63 children and adolescents treated with ATD increased by 25% for every additional 2 yr of treatment. Unfortunately, there is a lack of prospective long-term clinical studies evaluating of the efficacy of short- and long-term ATD therapy for increasing the remission rate in children. Additional studies are therefore required to increase our knowledge of ATD treatment in children. The use of ATD as a first-line treatment is widely accepted, but the optimal duration of ATD therapy before definitive treatment has not been determined.

The aim of this study was to assess the effect of the duration of carbimazole therapy on GD remission in children, after three consecutive courses of ATD therapy, with the discontinuation of treatment after each cycle.

Patients and Methods

Patients and protocol

This prospective cohort study included all consecutive patients aged up to 18 yr with GD seen at the centers of a French nationwide network between 1997 and 2002. The study population at presentation has been described elsewhere (14). The intention was to offer ATD treatment, preferably with carbimazole, for three consecutive cycles of 2 yr in cases of hyperthyroidism relapse after the discontinuation of treatment at the end of a cycle. Outcome after each course of ATD was defined as successful with remission, or relapse. In cases of hyperthyroidism relapse, patients began another 2-yr cycle of ATD treatment. The final time point for this study was March 2010.

During follow-up in this observational study, we noted whether patients were euthyroid in remission or euthyroid on ATD treatment or had developed a relapse of hyperthyroidism after the cessation of ATD therapy. In cases of poor compliance with ATD treatment, at the patient's initiative, with clinically identified relapses of thyrotoxicosis, or in cases of major adverse effects of ATD treatment (hepatotoxicity or severe allergic reaction) requiring ATD discontinuation, definitive reatment (radioiodine or thyroidectomy according to the medical indication or preference of the patients) was performed.

Method

Recorded at diagnosis, before treatment initiation, were age, sex, ethnicity, findings of an auxological and pubertal assessment, and presence of signs of clinical severity of GD based on the presence of at least two of the following features: tachycardia (pulse rate $>$ 100/min), hypertension, initial weight loss ($\geq$1 kg), or ophthalmic abnormalities (exophthalmos and/or upper lid retraction), presence and size of goiter, thyroid peroxidase autoantibody (TPOAb) status, and serum concentrations of free T_4 (FT_4), FT_3, and TRAb. Medical history, the presence of associated overt autoimmune disease, and a family history of hyperthyroidism (first- and second-degree relatives), if any, were recorded at diagnosis and during follow-up.

The starting dose and management of ATD treatment during follow-up, clinical and laboratory test results, and outcome after the first course of ATD have already been reported (14). Because no additional benefit accrues from the maintenance of high doses of ATD combined with replacement doses of L-T_4 (18, 20), all decisions concerning the management of L-T_4 treatment were made on an individual basis. Information was also recorded regarding the duration of ATD treatment and the resumption of treatment, together with the outcome or timing of definitive treatment.

Remission was defined as at least 18 months of euthyroidism after the cessation of ATD therapy. Relapse was defined as the presence of hyperthyroidism with TSH suppression (TSH $<$0.05 mIU/liter) combined with serum FT_4 concentrations greater than 21 pmol/liter or FT_3 concentrations greater than 11 pmol/liter.

The main endpoint was remission for at least 18 months after the completion of each course of treatment, taking into account two potentially competing events: definitive treatment and the continuation of ATD treatment. Patients still on ATD treatment were not considered to be relapse free.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol was reviewed and approved by the Clinical Research and Development Department of Assistance Publique-Hôpitaux de Paris and by the Paris Ile de France IV ethics committee. It was explained to all subjects and their parents, who signed an informed consent form for participation. The study (which started in 1997) was not registered in a public database for clinical studies (clinical trial.org or others) because it was considered to be an observational study.

Statistical analysis

Results are expressed as numerical values (percentages) for categorical variables and as medians (25–75th percentiles) for continuous variables. Comparisons of the characteristics of different groups of patients at onset were based on χ^2 tests or Fisher's exact tests for categorical variables and Wilcoxon tests for continuous variables.

The time to occurrence of remission was estimated by calculating cumulative incidence, considering the occurrence of definitive treatment and the continuation of ATD treatment as competing risks (21). Data for patients were censored if the patients were last seen more than 2 yr before March 2010, when they were still on ATD treatment. The start of ATD treatment was used to calculate the time to each event until 1) 18 months after the end of the last course of treatment in the absence of relapse, 2) the date of surgery or iodine therapy for definitive treatment, or 3) the date of the last follow-up, within a window of 2 yr before March 2010, for patients still on ATD treatment. ATD treatment was continued if patients suffered a relapse after the discontinuation of treatment or because they or their parents preferred to continue treatment. We also carried out a sensitivity analysis, considering patients lost to follow-up as still on ATD treatment.

The variables associated with remission were analyzed with the regression model for subdistributions of competing risks developed by Fine and Gray (22). The following variables were studied: age, sex, ethnicity, weight [SD score (SDS)], height (SDS), BMI (SDS), pubertal stage, personal history of overt autoimmunity and susceptibility factors, family history of hyperthyroidism, severe initial clinical presentation, goiter, FT_4, FT_3, TRAb, and TPOAb. The distribution of missing data was considered to be random, and multiple imputations were therefore carried out with PROC MI and MI-ANALYSE in SAS version 9.2, making it possible to analyze complete cases. We identified cutoff points defining severity levels for each continuous covariate (FT_4 and TRAb) by carrying out nonparametric spline estimation with the generalized additive model procedure (23). The cutoff points were used to define dummy variables for the individual levels of each variable.

Variables with a P value <0.3 in bivariate analysis were entered into the initial multivariable model, to which stepwise backward-forward selection was then applied. The results are expressed as subhazard ratios (SHR) with 95% confidence intervals (CI). All tests were two-tailed.

Statistical analyses were performed with the SAS version 9.2 (SAS Inc., Cary, NC) software package.

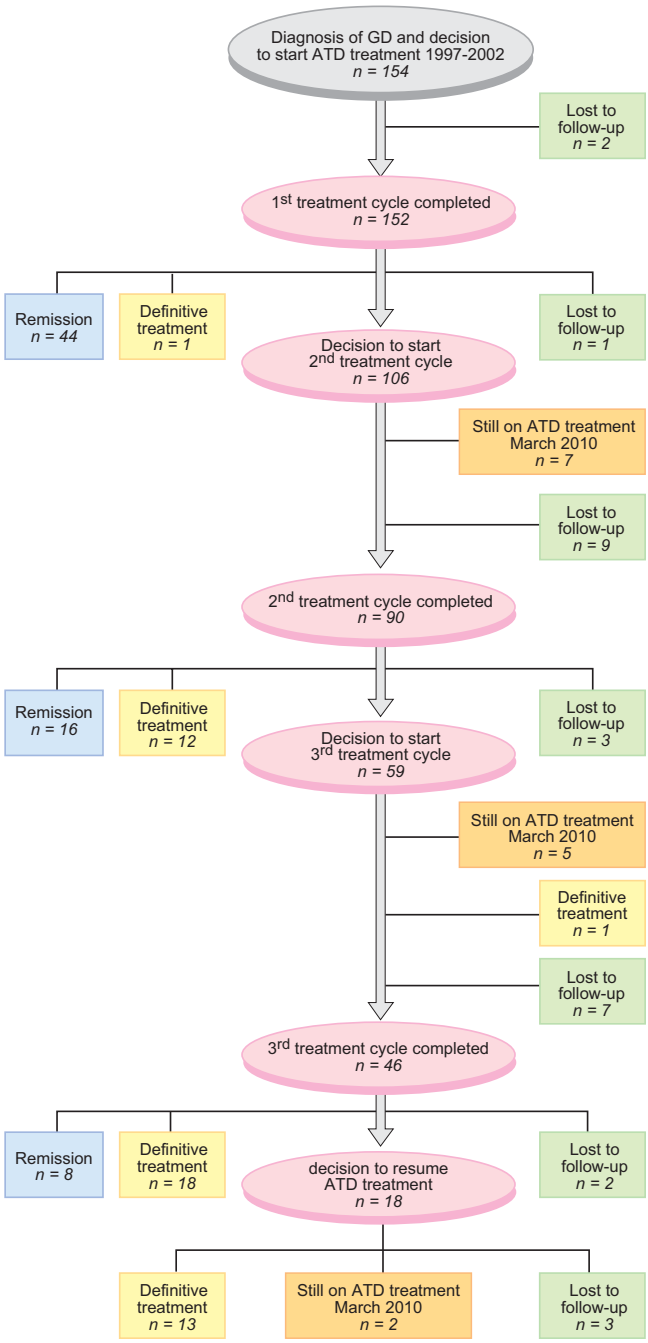


FIG. 1. Flow chart showing the completion of each course of ATD treatment and type of outcome groups. Data for the first treatment cycle have been updated with respect to our previous report (14).

Results

The median duration of follow-up was 10.4 (9.0–12.1) yr. Patients were categorized according to the type of outcome as in remission (n = 68), undergoing definitive treatment (n = 45), or continuing ATD treatment (n = 14). Data were censored for 27 patients who were lost to follow-up for at least 2 yr during medical treatment (Fig. 1). The characteristics of the patients at presentation and during management are shown, by outcome group at the end of follow-up, in Tables 1 and 2. Three serious adverse effects of ATD treatment were reported, requiring definitive treatment 2 months and 3 and 7 yr after the start of ATD treatment, due to allergic reaction (n = 1), neutropenia (n = 1), and arthralgia (n = 1), respectively.

Overall estimated remission rates (95% CI) 18 months after the withdrawal of ATD treatment increased with time and were 20 (13–26), 37 (29–45), 45 (35–54), and 49% (40–57%) after 4, 6, 8, and 10 yr of follow-up, respectively (Fig. 2). The estimated proportions of patients undergoing definitive treatment or still receiving ATD

TABLE 1. Characteristics of the children with GD at presentation, according to the type of outcome at the end of follow-up

	Remission	Definitive treatment	Still on ATD treatment	Lost to follow-up
n	68	45	14	27
Age (yr)	12 (8–14)	12 (10–13)	11 (7–13)	13 (10–15)
≤10 yr	24 (35)	9 (20)	6 (43)	4 (15)
>10 yr	44 (65)	36 (80)	8 (57)	23 (85)
Sex				
Female	51 (75)	34 (76)	11 (79)	22 (81)
Male	17 (25)	11 (24)	3 (21)	5 (19)
Ethnicity				
Non-Caucasian	15 (22)	7 (15)	2 (14)	7 (26)
Caucasian	53 (78)	38 (85)	12 (86)	20 (74)
Height SDS	0.98 (0.11–2.04)	1.11 (−0.02–2.04)	0.95 (0.41 − 1.78)	1.25 (0.24 − 1.89)
Body mass index SDS	−0.54 (−1.27–0.41)	−0.66 (−1.59–0.19)	− 0.30 (− 1.10 to − 0.60)	−0.20 (−1.00–0.30)
Pubertal development				
Prepubertal (Tanner 1)	28 (41)	19 (42)	7 (50)	11 (41)
Pubertal (Tanner 2–5)	40 (59)	26 (58)	7 (50)	16 (59)
Personal history of autoimmunity or susceptibility factors[a]	15 (22)	3 (7)	2 (14)	2 (7)
Family history of hyperthyroidism[b]	15 (23)	13 (28)	5 (36)	5 (19)
Severe initial clinical presentation[c]	42 (62)	37 (82)	14 (100)	16 (59)
Goiter				
Absent or small	24 (44)	18 (43)	8 (61)	13 (50)
Moderate or large	36 (56)	24 (57)	5 (39)	13 (50)
FT_4 (pmol/liter)	50 (37–71)	51 (44–70)	59 (49–79)	52 (36–68)
<35	15 (23)	4 (9)	0 (0)	5 (19)
≥35	52 (77)	40 (91)	14 (100)	22 (81)
FT_3 (pmol/liter)	26 (15–30)	26 (19–33)	26 (19–30)	22 (14–40)
<10	5 (9)	1 (3)	1 (10)	1 (4)
≥10	51 (91)	38 (97)	9 (90)	22 (96)
Multiple of normal upper limit for TRAb	4 (2–10)	2 (1–5)	7 (4–10)	3 (1–10)
TPOAb positivity	36 (62)	34 (77)	9 (69)	20 (77)

Results are shown as median (25–75th percentile) or number (percent).

[a] Type 1 diabetes (n = 9), idiopathic thrombocytopenic purpura (n = 1), trisomy 21 (n = 7), trisomy 18 (n = 1), DiGeorge syndrome (n = 3), and type 1 diabetes plus trisomy 21 (n = 1).

[b] First-degree relative(s) (n = 18), second degree relative(s) (n = 17) and both first- and second-degree relatives (n = 2).

[c] Severe initial clinical presentation is defined by the presence of at least two of the following features: tachycardia, hypertension, initial weight loss, and ophthalmic abnormalities.

treatment were 36 (28–45) and 11% (5–17%), respectively, after 10 yr of follow-up.

The multivariable competing risk model according to outcome revealed an independent positive effect on remission after medical treatment of less severe forms of hyperthyroidism at diagnosis, as evaluated by serum FT_4 concentration [SHR of 1 for patients with FT_4 <35 pmol/liter *vs.* 0.4 (0.20–0.80) for $FT_4 \geq 35$ pmol/liter; $P = 0.01$] and of the presence of other autoimmune conditions [SHR of 2.23 (1.19–4.18); $P = 0.01$] (Table 3). By contrast to our previous report concerning the risk of relapse after the first course of treatment, no independent effect on long-term remission rate of ethnicity, age, or serum TRAb levels at diagnosis was observed. Being at least 10 yr old at diag-

TABLE 2. Characteristics of patient management by type of outcome at the end of follow-up

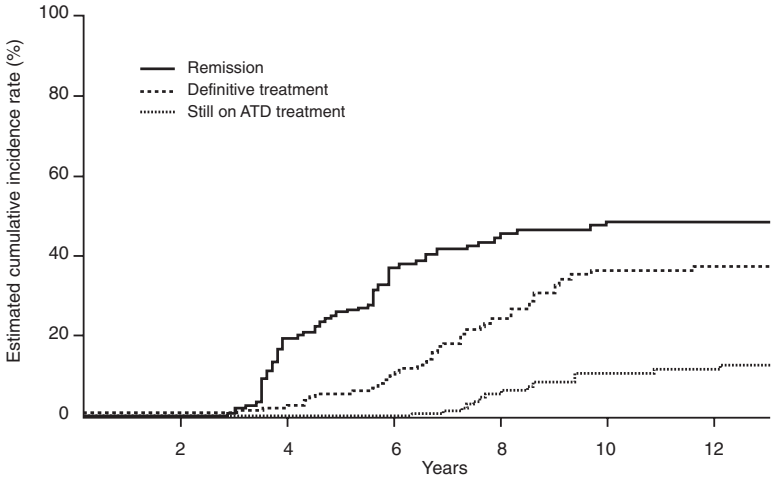
	Remission	Definitive treatment[a]	Still on ATD treatment	Lost to follow-up
n	68	45	14	27
Number of treatment cycles (number of patients)				
One	44	1	0	3
Two	16	12	7	12
Three	8	32	7	12
Duration of treatment cycle (months)				
First	24.9 (23.7–29.0)	24.6 (23.5–26)	24.4 (22.0–27.2)	25.0 (22.9–31.0)
Second	25.1 (23.7–30.8)	24.4 (21.6–28.7)	24.2 (20.7–26.3)	23.6 (17.9–33.9)
Third	24.4 (9.5–31.6)	18.1 (7.2–26.6)	17.3 (2.9–31.7)	27.9 (27.2–30.2)
Age at first cycle initiation (yr)	11.9 (8.5–14.0)	11.8 (10.1–13.4)	11.0 (7.3–13.4)	13.1 (10.4–14.9)
Age at second cycle initiation (yr)	13.2 (8.8–15.1)	14.3 (12.8–16.1)	13.6 (9.6–16.5)	15.9 (13.0–17.5)
Age at third cycle initiation (yr)	13.8 (11.9–16.4)	16.7 (14.7–17.9)	13.9 (9.4–20.1)	15.4 (10.0–18.5)
Age at last treatment withdrawal, definitive treatment, or last time point, respectively (yr)	15.4 (12.4–17.1)	19.1 (16.1–20.2)	18.0 (15.5–21.5)	16.8 (14.3–19.2)

Results are shown as median (25–75th percentile) or number (percent).

[a] Iodine treatment (n = 14) or thyroidectomy (n = 31).

nosis was an independent predictor of definitive treatment [SHR of 2.46 (1.12–5.40); $P = 0.02$]. The presence of other autoimmune conditions [SHR of 7.92 (1.32–47.32); $P = 0.02$] and being female [SHR of 4.27 (0.80–22.65); $P = 0.08$] were independent predictors of a longer duration of medical treatment, although this second predictor was of borderline significance in this multivariable analysis (Table 3). Considering patients lost to follow-up as still on ATD treatment had no effect on the factors influencing remission and only slightly modified remission rates at 8 yr [median remission rate of 42% (34–48%)] and 10 yr [median remission rate of 44% (36–51%)].

A comparison of patients with and without coexisting autoimmune conditions showed that the proportion of female patients was smaller, serum thyroid hormone concentrations were slightly lower, and goiter was more frequently small or absent in patients with other autoimmune conditions than in patients without autoimmune conditions (Table 4).



Probability estimate (95% CI)	2	4	6	8	10	12
Remission	0	0.20 (0.13-0.26)	0.37 (0.29-0.45)	0.45 (0.37-0.54)	0.49 (0.40-0.57)	0.49 (0.40-0.57)
Definitive treatment	0.01 (0-0.02)	0.03 (0-0.05)	0.12 (0.07-0.17)	0.24 (0.17-0.32)	0.36 (0.28-0.45)	0.37 (0.29-0.46)
Still on ATD treatment	0 -	0 -	0 -	0.06 (0.02-0.10)	0.11 (0.05-0.17)	0.12 (0.06-0.18)
Number of patients lost to follow-up n=27	*2*	*7*	*4*	*10*	*4*	*0*

FIG. 2. Cumulative incidence of remission, definitive treatment, and continuing ATD treatment estimated by competing risks models. Data are plotted from the start of the first course of ATD treatment until the event of remission (18 months after the last ATD treatment), definitive treatment, or continuing ATD treatment at the last time point.

Discussion

In a recent report on this prospective longitudinal study, we showed that the overall estimated relapse rate for hyperthyroidism was 68% 2 yr after the end of the first course of ATD. An association was found between ethnicity, age, and disease severity at diagnosis on the one hand and the risk of relapse after the end of the first course of ATD treatment on the other (14). Here, we investigated the effect of treatment duration after three consecutive courses of ATD therapy. We found that about half the patients achieved remission after the discontinuation of carbimazole, with a

TABLE 3. Multivariable competing risk model for determining the association between individual variables and the three outcome groups

	Remission, n = 68		Definitive treatment, n = 45		Still on ATD treatment, n = 14	
	SHR (95% CI)	*P*	SHR (95% CI)	*P*	SHR (95% CI)	*P*
Sex						
Male	1		1		1	
Female	1.38 (0.77–2.47)	0.28	1.57 (0.76–3.24)	0.23	4.27 (0.80–22.65)	0.08
Age at diagnosis (yr)						
≤10 yr	1		1		1	
>10 yr	0.99 (0.59–1.67)	0.98	2.46 (1.12–5.40)	0.02	1.53 (0.43–5.48)	0.52
Personal history of autoimmunity or susceptibility factors						
No	1		1		1	
Yes	2.23 (1.19–4.18)	0.01	1.03 (0.30–3.47)	0.96	7.92 (1.32–47.32)	0.02
FT_4 at diagnosis (pmol/liter)						
<35	1		1		1	
≥35	0.40 (0.20–0.80)	0.01	0.91 (0.27–3.09)	0.89	–[a]	–[a]

Variables not independently associated with the three types of outcome and not retained in the final model included ethnicity (Caucasian *vs.* non-Caucasian), severe initial clinical characteristics, body mass index SDS, pubertal development (prepubertal *vs.* pubertal), presence and size of goiter at presentation, family history of hyperthyroidism, and serum TRAb concentration at diagnosis.

[a] The test was invalid due to the small number of patients.

median study period of 10.4 yr and a very low frequency of adverse events related to carbimazole therapy. Careful multivariable analysis showed that lower serum FT_4 concentration at the time of diagnosis or the presence of other associated autoimmune conditions was associated with an increase (by a factor of about 2.2) in the predicted remission rate achieved with ATD treatment. Predictive variables associated with definitive treatment or the maintenance of ATD treatment at the last time point of the study period were less robust. This is probably because many clinicians treating pediatric patients are reluctant to recommend definitive therapy in younger patients (24), making age a confounding factor, and because there was only a limited number of events.

This study is unique in being based on a national sample of children with GD followed prospectively for a median of 10.4 yr. We retained in the final analysis those of the 154 patients originally included in this real-life study who did not follow the protocol due to hyperthyroidism recurrence after stopping treatment, those undergoing definitive treatment due to a lack of compliance with drug treatment or their own or their parents' preference, those who did not receive ATD treatment for the defined period of 24 ± 3 months, and those who did not stop ATD treatment after one course of ATD. In this study, the main endpoint of interest was time to remission, making it possible to study the factors associated with this event. The occurrence of definitive treatment during ATD treatment or the absence of an attempt to stop treatment after 24 months could have resulted in data being censored for the outcome of interest. However, this would imply that the censored data would not be informative in Cox model analysis. This assumption is untenable because definitive treatment prevents the spontaneous occurrence of remission. In this setting, standard survival methods are therefore no longer valid. The Fine and Gray model is based on the hazard associated with the cumulative incidence function. It therefore predicts the cumulative incidence of remission, which tends toward the prevalence of remission over time. The SHR estimated by the Fine and Gray model is based on the ratio of subdistribution hazards, and estimates of the separate effects of covariates on each outcome are provided by the model (22). The use of competing risk models therefore made it possible to take into account the occurrence rates for three dependent outcome types, with estimation of the risk of one type of outcome over time with the others. Despite deviation in some cases from the study protocol, the large size of the population studied made it possible to define the maximum duration for which ATD treatment could be considered beneficial, corresponding to the plateau in the number of remission events between 8 and 10 yr after the initiation of ATD therapy, and to identify factors predictive of the occurrence of a given outcome.

However, this study has several limitations. In this prolonged multicenter study, it was not possible to arrange blood sampling at a precise time for the entire follow-up period, and the levels of thyroid hormones and of TRAb and TPOAb before and after each course of ATD treatment were not available. It was also not possible to document compliance or all the potential adverse events due

TABLE 4. Characteristics of the patients at presentation and outcome according to the presence or absence of other overt autoimmune conditions

	Personal history of autoimmunity or susceptibility factors	No personal history of autoimmunity or susceptibility factors	*P* value
n	22	132	
Age (yr)	13.0 (8.9–14.6)	11.8 (9.4–13.7)	0.3
≤10 yr	6 (27)	37 (28)	0.9
>10 yr	16 (73)	95 (72)	
Sex			0.01
Female	12 (55)	106 (80.3)	
Male	10 (45)	26 (19.7)	
Ethnicity			0.05
Non-Caucasian	1 (5)	30 (23)	
Caucasian	21 (95)	102 (77)	
Height SDS	0.11 (−1.57–1.35)	1.11 (0.20–2.14)	0.001
Body mass index SDS	− 0.89 (− 1.23 to − 0.24)	−0.43 (−1.31–0.38)	0.6
Pubertal development			0.9
Prepubertal (Tanner 1)	9 (41)	56 (42.4)	
Pubertal (Tanner 2–5)	13 (59)	76 (57.6)	
Family history of hyperthyroidism	3 (14)	35 (27)	0.2
Severe initial clinical presentation	13 (59)	96 (73)	0.2
Goiter			0.0002
Absent or small	17 (85)	50 (40)	
Moderate or large	3 (15)	75 (60)	
FT_4 (pmol/liter)	50 (30–60)	54 (41–74)	0.06
<35	6 (27)	18 (14)	0.1
≥35	16 (73)	112 (86)	
FT_3 (pmol/liter)	18 (13–25)	27 (18–32)	0.02
<10	2 (13)	6 (5)	0.3
≥10	14 (87)	106 (95)	
Multiple of normal upper limit for TRAb	2.7 (1.4–6.1)	4.45 (1.5–9.3)	0.3
TPOAb positivity	16 (80)	83 (69)	0.3
At last outcome			0.09
Remission	15 (68)	53 (40)	
Definitive treatment	3 (14)	42 (32)	
Still on ATD treatment	2 (9)	12 (9)	
Lost to follow-up	2 (9)	25 (19)	

Results are shown as median (25–75th percentile) or number (percent).

to treatment objectively. Moreover, we cannot exclude the possibility that some of the patients in remission experienced a relapse of hyperthyroidism more than 18 months after the end of ATD treatment, as reported in adult studies, in which relapses may occur even 5 yr after the end of ATD treatment (25, 26). Overall, 17% of patients were lost to follow-up, but this had only a slight effect on remission rates at 8 and 10 yr and no effect on the risk factors identified, even if we considered these patients to be continuing ATD treatment. This high percentage of patients lost to follow-up is not particularly surprising given that patients are transferred from pediatric to adult units during this period. Given the observational nature of data collection and the increasing prevalence of autoimmune disorders with age, the proportion of patients with associated autoimmune conditions in this study is likely to be underestimated, because the patients were young. Moreover, some autoimmune diseases tend to occur early in life (*e.g.* type 1 diabetes), whereas others tend to occur later, in adulthood (*e.g.* rheumatoid arthritis, which was not found in this population of young patients) (27). It is therefore possible that some of our patients with GD will display other autoimmune disorders and/or predominantly Hashimoto thyroiditis later in life, given the associations between these two autoimmune thyroid diseases (28).

The mechanism underlying remission during treatment of a hyperthyroid state may be linked to the restoration of euthyroidism. Hyperthyroidism itself has been shown to perpetuate or even to worsen autoimmunity, leading to the generation of more TRAb and an aggravation of hyperthyroidism. Once this cycle is broken by ATD treatment rendering the patient euthyroid, the patient may experience gradual remission of the disease. This highlights the importance of rendering patients euthyroid and maintaining them in that state for long periods to minimize thyroid autoimmunity and GD recurrence (29, 30). Poor compliance with treatment, as often reported in long courses of treatment, particularly in adolescents (10, 31), and drug

discontinuation, with consecutive courses of ATD treatment rather than more prolonged continuous treatment, may compromise GD remission, as recently shown in a retrospective study in adult patients (32). A period of about 8 yr of ATD treatment was identified here as being fully beneficial. This is consistent with the findings of one previous retrospective study (19) but contrasts with other retrospective studies on limited numbers of pediatric patients treated with ATD for extended periods (9, 10, 12) and data for adult patients. These other studies have suggested that if remission is not achieved within 18 months of ATD treatment, definitive treatment should be pursued, because remission is unlikely to occur with longer periods of drug treatment (33).

Clinicians have long sought clinical and laboratory predictors for the identification of patients most likely to display remission after ATD treatment. Studies in adults have indicated that patients presenting more severe forms of the disease are less likely to achieve remission (16). We show here, for the first time in children, that the effect on remission of initial lower severity of the hyperthyroidism state, defined as lower initial serum FT_4 concentration, persists in the long term. These findings are consistent with the findings of our previous study in this population and the only other prospective study of short-term outcome in children (13). However, the results of the multivariate analysis in this long-term prospective study differed from the short-term results in showing no effect of age at presentation (13, 14) or of initial TRAb levels and ethnicity (14) in this population of patients with GD onset during childhood. The reason for this observed difference between our short- and long-term findings is unclear. However, although this is the largest prospective study carried out to date, it is possible that this lack of difference results from the limited number of subjects studied, resulting in a lack of statistical power. Like other autoimmune diseases, GD is probably caused by a combination of genetic and environmental factors that may also determine the long-term prognosis (28). Over time, the disease may fluctuate in activity, and some patients may become spontaneously euthyroid (34). Strong familial associations are observed, and GD is often found associated with other autoimmune disorders in a given subject (27). GD outcome has not previously been shown to differ as a function of coexisting autoimmune conditions in adult and pediatric populations (35, 36). However, in children with GD and Down's syndrome, opposite results were obtained in two independent populations, with the combination of these two conditions resulting in either a less or a more severe clinical course (37, 38).

The results of this prospective study highlight an interesting independent association with a significantly better outcome of the disease in patients with other autoimmune diseases, such as type 1 diabetes, or genetic conditions known to be associated with a high risk of coexisting autoimmune diseases, such as the Down's and DiGeorge syndromes, even when the slight differences in disease severity at presentation are taken into account (37, 39). The difference in height SDS at GD presentation was probably accounted for by some of these conditions (Down's syndrome). However, as in other studies (27, 37, 38), we found significant differences in the proportions of patients with coexisting conditions between boys and girls, with a lower predominance of female patients with coexisting autoimmune conditions.

In conclusion, this study suggests that children with GD displaying good compliance with treatment and without major adverse effects of ATD medication may be offered up to 8–10 yr of medical treatment with ATD before definitive treatment is envisaged. However, continuous treatment, rather than treatment cycles of 2 yr, should be considered in future clinical trials. This would make it possible to determine the positive impact and optimal duration of a long period of primary ATD treatment on outcome. Long-term therapy should also be optimized by educational strategies, to improve compliance with treatment and medical care, particularly during the transition from pediatric to adult services. Our findings also highlight the importance of screening for other autoimmune conditions if children present specific symptoms at diagnosis or during the course of GD. The results of this study require validation in other cohorts of patients, but the stratification of patients according to initial severity and the presence of other autoimmune conditions would improve the management of these patients. Additional studies throughout childhood and adulthood are required, even after the discontinuation of drug therapy and after other alternative treatments. This is particularly important given the increasing prevalence of autoimmune disorders with age in this predisposed population (27), potential pregnancy complications, and/or adverse effects on the offspring of maternal thyroid disorders or ATD medication (40), together with possible consequences for the health-related quality of life of patients (41).

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