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Duration of anti-thyroid drugs treatment in Graves'Disease in children

Pr Juliane Léger
Paediatric Endocrinology Department
Paris Diderot University
Hôpital Robert Debré, Paris, France

Disclosure

Nothing to disclose

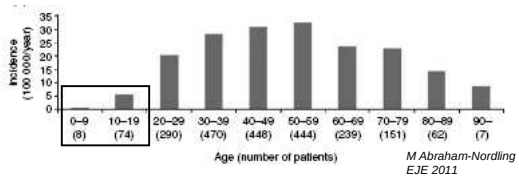
Duration of anti-thyroid drugs treatment in Graves'Disease in children

Learning objectives

- Feel confident establishing antithyroid drug treatment in GD during childhood
- Manage ATD treatment in children
- Identify children at risk of relapse after 2 years of ATD treatment
- Recognize factors predicting the likelihood of remission after long term drug treatment during childhood
- Identify the management options and choose risk-adapted treatment strategies

Graves'disease in childhood

- Incidence rare: about 1/5000



M Abraham-Nordling EJE 2011

- Graves'disease (>95%) Ac anti-R-TSH +
  - Pathogenesis: interaction genetic background + environnemental factors and the immune system
  - More frequent in ♀, familial form (20%)
  - Various symptoms of hyperthyroidism

Graves'disease in childhood

- Optimal management: no evidence based strategy
- Most patients initially treated at least 2 yrs with antithyroid drug (ATD) Debate about duration of ATD treatment
- Fewer than 30% of children achieve lasting remission after about 2 years of ATD Tt.
- Alternative treatment: thyroidectomy, Radioiodine
  - relapse after an appropriate course of ATD
  - lack of compliance
  - ATD toxicity

Antithyroid drug therapy

Major advantage

- Normal homeostasis of the hypothalamic-pituitary-thyroidal axis may be restored
- Period of medical treatment may be followed by freedom from medical intervention
- However, considerable time may be required to achieve remission
- and a substantial proportion of patients do not have remission

Antithyroid drug therapy

- Adults: no evidence to suggest that extending ATD Treatment beyong 18 months is of benefit
- Children: longer ATD treatment courses than in adults

Graves'disease in childhood Recommandations

Methimazole-Carbimazole
0.1-1 mg/k/d

Some side effects dose dependent

- Use low doses
- Avoid block and replace
- Frequent clinical monitoring: every 3 to 4 months

Antithyroid drug therapy

Potential adverse events

	Carbimazole or methimazole	Propylthiouracil
Major side-effects (rare)	Agranulocytosis (0·2–0·5%), cholestatic hepatitis, teratogenic effects: choanal atresia and aplasia cutis, aplastic anaemia, thrombocytopenia, and hypoglycaemia (anti-insulin antibodies)	Agranulocytosis (0·2–0·5%), toxic hepatitis and fulminant liver failure, ANCA-positive vascultis, aplastic anaemia, thrombocytopenia, and hypoprothrombinaemia
Common minor side-effects (1–5%)	Urticaria or other rash, arthralgia, fever, and transient granulocytopenia	Urticaria or other rash, arthralgia, fever, and transient granulocytopenia
Uncommon minor side-effects (<1%)	Nausea and vomiting, abnormalities of taste or smell, and arthritis	Nausea and vomiting, abnormalities of taste or smell, and arthritis

Franklyn JA et al. Lancet 2012

Graves'disease in childhood Recommandations

PTU: risk of severe and fulminans hepatitis

- PTU should NEVER be used as first line treatment in children
- PTU use should only be considered in rare circumstances, such as preparation for surgery in a patient allergic to MMI, or in pregnancy
- Current PTU use in children taking this medication should be stopped in favor of alternative therapies

Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association of Clinical Endocrinologists. Thyroid 2011; 21: 593-646

MMI adverse Events of 100 treated children 17% minor; 2% major

Age at diagnosis	Gender	MMI dose at time of AE (mg/day)	Duration of therapy at time of AE	Reaction
3 5/12	M	10	12 weeks	Mild liver injury
4	M	10	32 weeks	Myalgias/joint pain/facial urticaria
4 4/12	F	10	2 weeks	Pruritis and hives
4 3/4	F	30	2 weeks	Stevens-Johnson syndrome
5 1/12	F	7.5	3 weeks	Diffuse urticaria
7 10/12	F	15	4 weeks	Arthralgia
8 2/12	F	10	2 weeks	Rash and joint pain
8 4/12	F	10	3 weeks	Urticaria
8 5/12	M	20	9 weeks	Arthralgia
8 10/12*	M	10	18 months	Neutropenia (ANCA+)
8 10/12*	M	10	18 months	Neutropenia (ANCA−)
10 7/12	M	40	4 weeks	Myalgias
11 1/2	F	20	4 weeks	Lymphopenia and eosinophilia
12 5/12	F	20	12 weeks	Myalgias
12 6/12	F	30	12 weeks	Stevens-Johnson syndrome (hospitalization)
14 2/12	F	30	4 weeks	Stevens-Johnson, syndrome
15 4/12	F	30	2 weeks	Rash
16 11/12	F	20	4 weeks	Rash on arms and face
17 6/12	F	30	3 weeks	Pruritic rash

Rivkees S Int J Pediatr Endocrinol 2010

Predictors of Relapse/Remission in children

- *B Lippe. (1985)*
  - Prolonged duration of Tt of ATS treatment. Study suggested a remission rate of approximately 25% with every 2 years of medical treatment
- *Glaser NS, Styne DN. JCEM 1997* (n = 191 but 85 excluded)
  - Goiter medium/large and BMI <-0.5SDS vs no goiter and BMI >0,5 SDS remission 13% vs 86%
- *Glaser NS, Styne DN. Pediatrics 2008* (n = 50)
  - high initial FT4 and FT3 levels
  - no euthyroidism within 3 months of ATD therapy
- *Lazar L et al. JCEM 2000* (n = 40)
  - Prepubertal vs pubertal (ns)

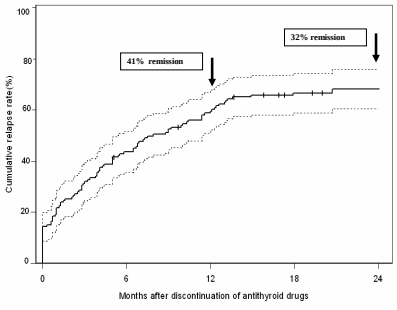
⇨
- *Mostly retrospective studies, limited number of patients*
- *Short and no-standardized follow-up, lost to follow-up, missing data +*

Cumulative incidence of relapse after 2 yrs of ATD Tt

Observational prospective follow-up cohort study n = 154 children

All patients initially treated with ATD for 3 consecutive cycles of 2 yrs in cases of relapse after discontinuation of Tt at the end of a cycle

- 87 / 99 relapses occur in the first year of follow-up
- Cumulative incidence of relapse:
  - ✓ at 1 year = 59%
  - ✓ at 2 years = 68%
- Median time to relapse = 8 months



F Kaguelidou et al. JCEM 2008

Predictors of thyrotoxicosis relapse after 2 years of ATD drugs in children

- Multivariable analysis (Cox proportionnal hazards model)

Variable	HR (95% CI)	*p*-value
Ethnicity (non Caucasian)	→ 2,54 (1,50 - 4,30)	0,0005
Age (5-yrs increment)	→ 0,74 (0,56- 0,97)	0,03
fT4 (10 pmol/l increment)	→ 1,18 (1,07- 1,30)	0,001
ATD treatment duration (12 months increment)	→ 0,57 (0,39- 0,84)	0,005
Multiples of upper normal limit for TRAb at onset (10-unit increment)	→ 1,21 (1,02- 1,45)	0,03

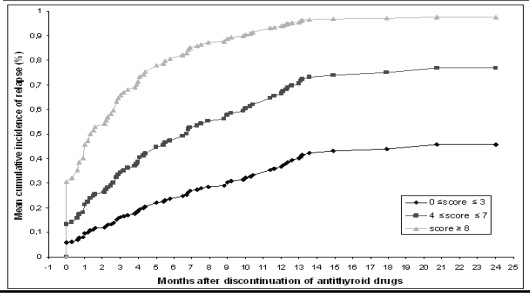
No influence on relapse :

gender, goiter size, BMI (SDS), family history of hyperthyroidism or personal history of autoimmunity

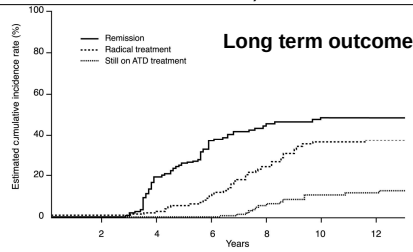
F Kaguelidou et al. JCEM 2008

Predictive score for recurrence risk

Prognostic score (0-11)	0	1	2	3
Ethnicity	Caucasian		Non Caucasian	
Age	> 12 years	5- 12 years	<5 years	
fT4 serum concentration	< 50 pmol/l			≥ 50 pmol/l
Multiples of upper normal limit for TRAb	≤ x 4 (N)	> x 4 (N)		
Duration of ATD treatment	> 24 months			≤ 24 months



Cumulative incidence of remission, radical Tt or still on ATS



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)
Radical 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 censored patients n=27	2	7	4	10	4	0

J Léger et al. JCEM 2012

Multivariate competing risk model for determining the association between individual variables and the three outcome groups

		Remission n = 68	Radical Tt n = 45	Still on ATD Tt n = 14
		Sub HR (IC95%)	Sub HR (IC95%)	Sub HR (IC95%)
Sex	Male	1	1	1
	Female	1.38 (0.77-2.47)	1.57 (0.76- 3.24)	4.27 (0.80- 22.65)
Age at diagnosis	≤10 yrs	1	1	1
	>10 yrs	0.99 (0.59-1.67)	2.46 (1.12-5.40)*	1.53 (0.43-5.48)
Personal history of autoimmunity or susceptibility factors	No	1	1	1
	Yes	2.23 (1.19-4.18)**	1.03 (0.30-3.47)	7.92 (1.32-47.32)*
FT4 at diagnosis	<35 pmol/l	1	1	‡
	≥35 pmol/l	0.40 (0.20-0.80)**	0.91 (0.27-3.09)	

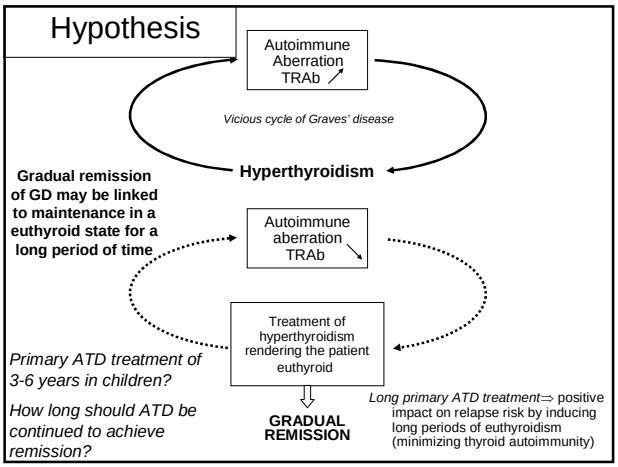
‡The test is invalid due to the low number of patients
HR: hazard ratio
* P = 0.02 **p = 0.01

J Léger et al. JCEM 2012

Graves'disease in childhood Long term outcome Prognostic risks

Unfavorable	Favorable
Biochemichal severity	Presence of other autoimmune conditions
Younger age	Older age
Large goiter	Duration of ATD treatment (> 2 years)
Non caucasians	
Non compliance to ATD	

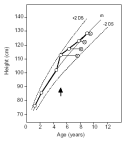
Hypothesis



Two cases of children with Graves'disease

3.5 years old boy

- Typical symptoms of hyperthyroidism (3 months)
  - weight loss
  - insomnia-nervousness- changes in behaviour
- Large diffuse goiter
  HR : 120/min
  Proptosis, staring eyes, retraction of the upper lid
- Increase in height velocity with advanced bone age



3.5 year old boy

- TSH <0.05 mui/L
- FT4 : 86 pmol/L
- FT3 : 30 pmol/L
- TRAb : 27 UI

⇨ Graves'disease

Methimazole 10 mg/d (0.6 mg/kg/d)

3.5 year old boy with Graves'disease

First course ot ATD treatment

Age (yrs)	FT4 (pmo/l)	TSH (mUI/L)	NMZ (mg/d)	NMZ (mg/kg/d)
3.5	86	0.02	-	-
4.3	12.3	4.3	5	0.3
4.7	23.6	0.06	5	0.3
5	9.1	34.7	7.5	0.4
5.3	10.4	8.9	6	0.35
5.9	13.2	12.5	5	0.25

FT4: N 9-21 pmol/L

TRAK; N <1

⇨ How would you manage him?

6 year old boy

- Relapse after 1.5 months of Tt withdrawal

FT4: 56 pmol/l; TSH: <0.05 mUI/L

⇨ How would you manage him?

6 year old boy with GD

Second course ot ATD treatment

Age (yrs)	FT4 (pmo/l)	TSH (mUI/L)	NMZ (mg/d)	NMZ (mg/kg/d)
6.1	14.5	<0.05	7.5	0.40
6.3	8.6	57	7.5	0.40
7	11.9	12	5	0.25
7.2	15.5	1.6	5	0.25
7.5	13.4	2.0	2.5	0.12

⇨ How would you manage him?

11 year old boy

- Treatment was stopped at 8 yrs old
- Relapse after 3 years of Tt withdrawal

FT4: 24 pmol/L; FT3: 10 pmol/L; TSH: <0.05 mUI/L

FT4: N 9-21 pmol/L
FT3: N 3-7pmo/L

TRAK; N <1

⇨ How would you manage him?

15.3 year old boy

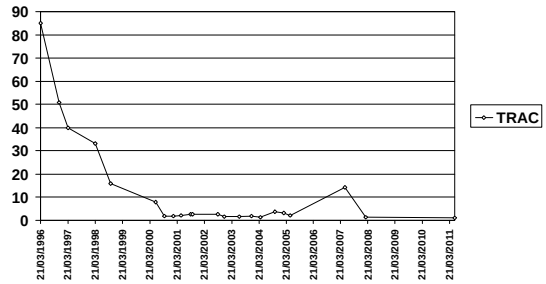
Third course ot ATD treatment

Age (yrs)	FT4 (pmo/l)	TSH (mUI/L)	NMZ (mg/d)	NMZ (mg/kg/d)
11	14.5	<0.05	5	0.16
12.5	13.6	2.6	5	0.15
14.5	15.4	2.3	5	0.13
15.3	13.9	3.6	2.5	0.05

⇨ Graves'disease

How would you manage him?

Evolution TSH-R antibodies



20 year old boy

- Treatment withdrawal at 15.5 yrs
- 19.7 yrs old: still on remission

⇨ What would you recommend to him?

5 year old girl with Graves'disease

- TSH <0.05 mui/L
- FT4 : 92 pmol/L
- FT4 : >31 pmol/L
- TRAb : 31 UI

5 year old girl

First course ot ATD treatment

Age (yrs)	FT4 (pmol/l)	FT3 (pmol/l)	TSH (mUI/L)	TRAk (UI/L)	NMZ (mg/d)	NMZ (mg/k/d)
5.0	92	>31	<0.02	31	-	-
5.3	20.5	10.4	<0.02	-	15	0.8
5.5	12.9	7.8	<0.02	15	20	1
5.8	17.6	9.6	0.03	27	20	1
6.0	19.5	10.2	<0.01	23	25	1.1
6.3	10	5.2	2.5	12	30	1.2
7.0	18.7	7.0	0.05	9	25	0.9

FT4: N 9-21 pmol/L
FT3: N 3-7pmo/L

TRAK; N <1

5 year old girl

First course ot ATD treatment, continued…

Age (yrs)	FT4 (pmol/l)	FT3 (pmol/l)	TSH (mUI/L)	TRAk (UI/L)	NMZ (mg/d)	NMZ (mg/k/d)
8.0	16	6.2	1.2	2.5	17.5	0.5
9.0	17.7	6.6	0.6	2.0	10	0.25

⇨ Graves'disease

How would you manage her?

T 3 predominant Graves'disease

Persisting TSH suppression and clinical signs of hyperthyroidism
Elevated serum T3 levels after serum T4 becomes normal or even low

- Main characteristics between T3 predominant and common type of GD
  - high titer level of serum anti-TSH-R antibody
  - high FT3 to FT4 ratio
  - large goiter size
- Prevalence higher in children (10%?) than in adults
- Type 1 and Type 2 iodothyronine deiodinase are overexpressed in the thyroid tissue but pathogenesis still unclear
- These patients require higher ATS dosage++ *Matsumoto C et al. EJE 2013*
- Whether these patients demonstatred a low likelihood of remission in the long term remains unknown

Duration of anti-thyroid drugs treatment in Graves'Disease in children

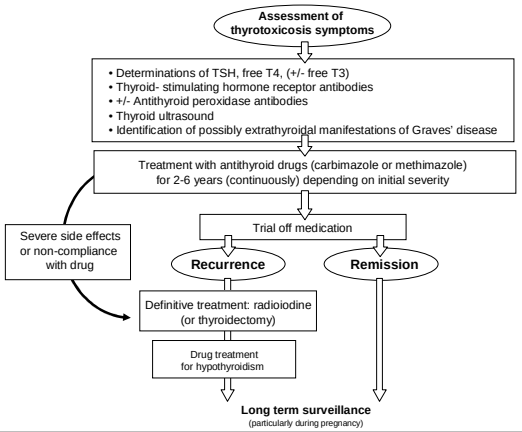
Conclusion

- The importance of maintaining euthyroid state by ATD for long periods with prolonged continuous rather than consecutive courses of Tt has been emphasized to minimize thyroid autoimmunity and GD recurrence
  P Laurberg, EJE 2006, Remission of GD, Time to reconsider the mechanism?

⇨Continued rather than ATD Tt cycles of 2 yrs ? *(future clinical trials)*
Duration of ATD: 2 to 6 years depending of the initial severity

- Long term therapy should be optimized by educational strategies to improve compliance
- Importance of screening for other autoimmune conditions
- Validation in other cohorts of patients

Algorithm for diagnosis and management of GD in children



Duration of anti-thyroid drugs treatment in Graves'Disease in children

Take home messages

- Methimazole (or carbimazole) is usually recommended as the initial treatment and is generally well tolerated
- Undetectable TSH and normal or low FT4 = FT3 should be measured
  T3 predominant GD requiring higher ATS dosage
- Remission achieved in only 30% of children after a course of anti-thyroid drug treatment for about 2 years
- More prolonged anti-thyroid drug treatment may decrease relapse risk and increase the remission rate to up to 50%
- Tell the parents the benefits and risks of anti-thyroid drugs are still uncertain and that they have the option of radical treatment after ATD treatment

Duration of anti-thyroid drugs treatment in Graves'Disease in children

References

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