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

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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
- Graves’ disease (≥95%) Ac anti-R-TSH +
  - Pathogenesis: interaction genetic background +
    - environmental 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 beyond 18 months is of benefit
- Children: longer ATD treatment courses than in adults

Graves’disease in childhood

Recommendations

Methimazole-Carbimazole
0.1-1 mg/kd

Some side effects dose dependent
- Use low doses
- Avoid block and replace
- Frequent clinical monitoring: every 3 to 4 months

Potential adverse events

<table>
<thead>
<tr>
<th>Common minor side-effects (1-5%)</th>
<th>Uncommon minor side-effects (&lt;1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria or other rash, arthralgia, fever, and transient granulocytopenia.</td>
<td>Nausea and vomiting, abnormalities of taste or smell, and arthritis.</td>
</tr>
</tbody>
</table>

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

Predictors of Relapse/Remission in children

- B Lippe. (1985) - Prolonged duration of T1 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 15% 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

MMI adverse Events of 100 treated children

17% minor; 2% major

BLS: & t test Pediatr Endocrinol 2010
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

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

• Multivariable analysis (Cox proportional hazards model)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity (non Caucasian)</td>
<td>2.54 (1.70 - 4.30)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Age (5 yrs increment)</td>
<td>0.74 (0.56 - 0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>fT4 (10 pmol/l increment)</td>
<td>1.18 (1.07 - 1.30)</td>
<td>0.001</td>
</tr>
<tr>
<td>ATD treatment duration (12 months increment)</td>
<td>0.57 (0.39 - 0.84)</td>
<td>0.005</td>
</tr>
<tr>
<td>Multiples of upper normal limit for TRAb at onset (10 unit increment)</td>
<td>1.21 (1.02 - 1.45)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

No influence on relapse:
- gender, goiter size, BMI (SDS), family history of hyperthyroidism
- personal history of autoimmunity

Predictive score for recurrence risk

<table>
<thead>
<tr>
<th>Prognostic score (0-11)</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>Non Caucasian</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&gt; 12 yrs</td>
<td>12 yrs</td>
<td>&lt; 12 yrs</td>
</tr>
<tr>
<td>fT4 serum concentration</td>
<td>&gt; 50 pmol/l</td>
<td>50 pmol/l</td>
<td>&lt; 50 pmol/l</td>
</tr>
<tr>
<td>Multiples of upper normal limit for TRAb at onset</td>
<td>&gt; 4xULN</td>
<td>≤ 4xULN</td>
<td></td>
</tr>
<tr>
<td>Duration of ATD treatment</td>
<td>&gt; 24 months</td>
<td>24 months</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative incidence of remission, radical Tt or still on ATS

Long term outcome

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

<table>
<thead>
<tr>
<th>Remission n = 68</th>
<th>Radical Tt n = 45</th>
<th>Still on ATD Tt n = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1.38 (0.77-2.45)</td>
<td>1.57 (0.79-3.15)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 yrs</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;10 yrs</td>
<td>0.99 (0.36-3.05)</td>
<td>2.46 (1.03-6.00)</td>
</tr>
<tr>
<td>Personal history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>2.23 (1.10-4.54)</td>
<td>1.03 (0.41-2.65)</td>
</tr>
<tr>
<td>fT4 at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 pmol/l</td>
<td>1</td>
<td>0.40 (0.04-3.18)</td>
</tr>
<tr>
<td>≥35 pmol/l</td>
<td>0.91 (0.27-3.06)</td>
<td>1</td>
</tr>
</tbody>
</table>

Graves’ disease in childhood

Long term outcome

Prognostic risks

<table>
<thead>
<tr>
<th></th>
<th>Unfavorable</th>
<th>Favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical severity</td>
<td>Present of other autoimmune conditions</td>
<td></td>
</tr>
<tr>
<td>Younger age</td>
<td>Older age</td>
<td></td>
</tr>
<tr>
<td>Large goiter</td>
<td>Duration of ATD treatment (&gt; 2 years)</td>
<td></td>
</tr>
<tr>
<td>Non causcians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non compliance to ATD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

J Léger et al. JCEM 2012
Treatment of hyperthyroidism rendering the patient euthyroid

Vicious cycle of Graves’ disease

Gradual remission of GD may be linked to maintenance in a euthyroid state for a long period of time.

Autoimmune Aberration TRAb

Gradual remission of GD may be linked to maintenance in a euthyroid state for a long period of time.

Primary ATD treatment of 3-6 years in children?

How long should ATD be continued to achieve remission?

Hypothesis

Long primary ATD treatment ⇒ positive impact on relapse risk by inducing long periods of euthyroidism (minimizing thyroid autoimmunity)

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

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 of ATD treatment

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>FT4 (pmol/L)</th>
<th>TSH (mUI/L)</th>
<th>NMZ (mg/kg/d)</th>
<th>NMZ (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>86</td>
<td>0.02</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4.3</td>
<td>12.3</td>
<td>4.3</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>4.7</td>
<td>23.6</td>
<td>0.06</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>9.1</td>
<td>34.7</td>
<td>7.5</td>
<td>0.4</td>
</tr>
<tr>
<td>5.3</td>
<td>10.4</td>
<td>8.9</td>
<td>6</td>
<td>0.35</td>
</tr>
<tr>
<td>5.9</td>
<td>13.2</td>
<td>12.5</td>
<td>5</td>
<td>0.25</td>
</tr>
</tbody>
</table>

6 year old boy

Relapse after 1.5 months of T1 withdrawal
FT4: 56 pmol/l; TSH: <0.05 mUI/L

How would you manage him?
6 year old boy with GD

**Second course of ATD treatment**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>FT4 (pmol/L)</th>
<th>TSH (mUI/L)</th>
<th>NMZ (mg/d)</th>
<th>NMZ (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>14.5</td>
<td>&lt;0.05</td>
<td>7.5</td>
<td>0.40</td>
</tr>
<tr>
<td>6.3</td>
<td>8.6</td>
<td>57</td>
<td>7.5</td>
<td>0.40</td>
</tr>
<tr>
<td>7</td>
<td>11.9</td>
<td>12</td>
<td>5</td>
<td>0.25</td>
</tr>
<tr>
<td>7.2</td>
<td>15.5</td>
<td>1.6</td>
<td>5</td>
<td>0.25</td>
</tr>
<tr>
<td>7.5</td>
<td>13.4</td>
<td>2.0</td>
<td>2.5</td>
<td>0.12</td>
</tr>
</tbody>
</table>

How would you manage him?

11 year old boy

- Treatment was stopped at 8 yrs old
- Relapse after 3 years of T1 withdrawal

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

How would you manage him?

15.3 year old boy

**Third course of ATD treatment**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>FT4 (pmol/L)</th>
<th>TSH (mUI/L)</th>
<th>NMZ (mg/d)</th>
<th>NMZ (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>14.5</td>
<td>&lt;0.05</td>
<td>5</td>
<td>0.16</td>
</tr>
<tr>
<td>12.5</td>
<td>13.6</td>
<td>2.6</td>
<td>5</td>
<td>0.15</td>
</tr>
<tr>
<td>14.5</td>
<td>15.4</td>
<td>2.3</td>
<td>5</td>
<td>0.13</td>
</tr>
<tr>
<td>15.3</td>
<td>13.9</td>
<td>3.6</td>
<td>2.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Graves'disease

How would you manage him?

Evolution TSH-R antibodies

- TRAC

5 year old girl with Graves'disease

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

What would you recommend to him?

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

First course of ATD treatment

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>FT4 (pmol/L)</th>
<th>FT3 (pmol/L)</th>
<th>TRAK (UI/L)</th>
<th>TSH (mUI/L)</th>
<th>NMZ (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>92</td>
<td>&gt;31</td>
<td>31</td>
<td>0.02</td>
<td>15</td>
</tr>
<tr>
<td>5.5</td>
<td>20.5</td>
<td>10.4</td>
<td>&lt;0.02</td>
<td>15</td>
<td>0.8</td>
</tr>
<tr>
<td>5.8</td>
<td>17.6</td>
<td>9.6</td>
<td>0.03</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>6.0</td>
<td>19.5</td>
<td>10.2</td>
<td>&lt;0.01</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>6.4</td>
<td>10</td>
<td>9.2</td>
<td>2.5</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>7.0</td>
<td>18.7</td>
<td>7.0</td>
<td>0.05</td>
<td>9</td>
<td>25</td>
</tr>
</tbody>
</table>

FT4: N 9-21 pmol/L
FT3: N 3-7 pmol/L
TRAK: N <1

T3 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++
- Whether these patients demonstrated a low likelihood of remission in the long term remains unknown

MATSUMOTO C et al. EJE 2013

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 or 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

Presented at the 83rd Annual Meeting of the American Thyroid Association, October 16-20, 2013 (Juliane Léger)
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References

- Lauberg P. Eur J Endocrinol 2006; 168:137-144