Length of antithyroid regimens and relapsing rates of Grave’s Disease

Version 2

Author: Johan Hinz, Bachelor of Church Music
Supervisor: Eva Rask, Ph. D, senior lecturer
Örebro, Sweden
Abstract

Background
Grave’s Disease (GD) is an autoimmune disease where autoantibodies through receptor signalling stimulate the thyroid gland peroxidase to produce thyroxine (T4) and triiodothyronine (T3). Antithyroid drugs (ATD) act by inhibiting peroxidase to catalyse the production of T4 and T3. ATD have severe side-effects: agranulocytosis and liver damage.

Withdrawal of ATD therapy is affiliated with a 50% risk of relapsing GD. There is no consensus considering the optimal length of ATD therapy to minimise the relapse risk.

Aim
To investigate if there is a difference in relapse rate between patients diagnosed with GD treated with ATD for twelve in comparison with 18 months of ATD.

Method
In this retrospective cohort study 72 patients diagnosed with GD at Örebro University Hospital were identified by review of medical records. Among these patients 36 were treated with ATD for twelve months and 36 patients, matched by age to the first group, treated with ATD for 18 months. These groups were followed for 1.5 years and the frequency of relapsing GD was measured and compared using statistical methods.

Result
Among patients treated for twelve months 30.6% were relapsing at 1.5 years follow up, compared to 16.7% in the 18-month group, p-value 0.165.

Conclusion
According to the results, this study indicates that; to minimise the risk of relapsing GD, patients treated with ATD could benefit from an 18-month regimen rather than twelve months. But the difference was not statistically significant. Hence, question of this study needs to be evaluated further.
**Abbreviations**

T₄: thyroxine  
T₃: triiodothyronine  
TSH: thyroid-stimulating hormone  
GD: Graves’ Disease  
TSH-R: thyroid-stimulating hormone receptor  
TRAb: thyroid stimulating hormone receptor antibody  
ATD: antithyroid drugs  
TPO: thyroid peroxidase  
BR: block and replace  
ETA: European Thyroid Association  
GI: Group I, (twelve months therapy)  
GII: Group II, (18 months therapy)  
E/L: units/litre
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Background

Anatomy and physiology of the thyroid
The thyroid gland is a hormone-producing gland, situated inferior and bilateral to the thyroid cartilage [1]. The main products from the thyroid are thyroxine (T4) and triiodothyronine (T3). The production of these hormones is regulated by thyroid-stimulating hormone (TSH), secreted by the pituitary [2]. In the body tissue T4 and T3 induce the basal metabolism through regulation of lipid and carbohydrate metabolism [3]. At the level of hypothalamus and anterior pituitary T3 and T4 exert negative feedback on TSH by decreasing the secretion of TSH [2].

Grave’s Disease
In 1835 Robert James Graves first described the disease that later would bear his name [4]. As the most common cause of hyperthyroidism, the annual incidence of GD is 20-50 cases per 100,000 persons [5]. However, the incidence varies over different regions and countries [6]. The overall prevalence of GD is 1-1.5% but it is for yet unknown reasons far more common in women than in men [7]. Nyström et al. [8] showed that the incidence of hyperthyroidism in the Gothenburg area (Sweden) was 27.6 per 100,000 persons and year.

Grave’s Disease (GD) is an autoimmune disease and the symptoms are due to overproduction of T4 and/or T3 [7]. Signs and symptoms of GD include: weight loss, tremor, tachycardia, heart failure, dyspnea, sweating (warm skin), and eye symptoms [5]. If not treated, GD leads to increased mortality and morbidity [9]. Activation of the thyroid-stimulating hormone receptor (TSH-R) by antibodies stimulate the excess production of thyroid hormones by activation of downstream intracellular signals [10,11].

Young age, male gender and higher level of thyroid stimulating hormone receptor antibodies (TRAb) are factors known to predict the course of GD [11,12]. The risk of relapsing disease increases in these groups, but the value of TRAb levels as a tool to predict relapse in an individual has not been proven in a convincing way [13].

Principles of treating Grave’s Disease
Removing the thyroid gland by surgery, destruction of thyroid tissue by radioiodine, or medical treatment with antithyroid drugs (ATD) are the three options for managing GD
In Sweden, methimazole and propylthiouracil are approved for ATD treatment of GD [16].

The therapeutic effect of ATD is a consequence of their inhibiting actions against thyroid peroxidase (TPO) [17]. The protein TPO has a major role in the normal production of thyroid hormones, by acting as catalyst in several steps of T4 and T3 production [18].

Methimazole is afflicted with several side effects whereof some are potentially lethal. Most frequently reported side effects are rash and pruritus (4-6%) followed by arthralgias and gastrointestinal effects [19]. Severe side effects are uncommon and include agranulocytosis, polyarthritis and liver damage [20]. The potential risk of agranulocytosis motivates that patients under ATD therapy need to carry out a blood count, to evaluate levels of leucocytes and neutrophil granulocytes, in the occurrence of suspected infection and symptoms of fever and/or sore throat [21]. Propylthiouracil is often not the first drug of choice and share most of the side effects with methimazole[22].

There are two ATD treatment principals; block and replace (BR), where a high dose of ATD that completely blocks the production of thyroid hormones is combined with compensating levothyroxine, or titration of dose, also called monotherapy [10]. When monotherapy is used the production of T4 and T3 is lowered to an adequate level to support physiological needs [23]. In Sweden BR is traditionally preferred by most physicians [21]. Withdrawal of ATD treatment is by the European Thyroid Association (ETA) recommended after twelve to 18 months provided that TSH and TRAb levels have normalised [7]. Although, there is yet no consensus for the optimal length of ATD medication [24].

One disadvantage of ATD; specifically the withdrawal, is the frequent incidence of relapse of GD [19]. The risk of relapse after an initial treatment period with ATD is 50% [13]. The occurrence of relapse is most frequent around three to six months after withdrawal but the risk never ceases entirely, some patients will experience relapse decades after their first GD episode [19].

According to Allannic et al [25] there is a lower risk of relapsing GD when patients are treated with ATD 18 months in comparison to six months. Another study by Maugendre et al [26] has shown that there is no additional benefit of ATD treatment longer than 18 months. To present knowledge it is unclear whether the relapse rate of GD differs when using a twelve-month regimen of ATD compared to an 18-month regimen.

Since the beginning of 2016 the Department of Medicine at Örebro University Hospital uses a twelve-month regimen for GD treatment instead of the previous 18-month regimen, this change in treatment duration enables this study.
Aim
To investigate if there is a difference in frequency of relapsing GD between patients diagnosed with GD and treated with a new ATD twelve-month regimen in comparison to patients receiving 18 months of ATD therapy.

Question
Is there a difference in relapsing GD one and a half year post withdrawal of ATD between patients treated with ATD for twelve months and patients treated 18 months?

Methods
This retrospective medical record study comprises two groups of patients that have been diagnosed and treated at the Department of Medicine at USÖ.

Medical records labelled with International Statistical Classification of Diseases and Related Health Problems - Tenth Revision (ICD-10) code E.050, E059, E058 and E055 [27] were reviewed to identify patients to the two groups.

All medical records of patients who made their first visit at the outpatient clinic at the endocrine unit of the department during the period 2015-07-01 to 2018-12-31 with suspected GD were reviewed by the author. Of them; all patients whose GD diagnosis was verified by a physician, through medical examination, laboratory tests and imaging techniques, and who received ATD treatment, with either methimazole or propylthiouracil, for ten to 14 months either with BR or monotherapy were included. These patients constitute group I (GI) (table 1).

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Group I</th>
<th>Inclusion criteria</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First visit at clinic</strong></td>
<td>15.07.01-18.12.31</td>
<td>12.07.01-14.12.31</td>
<td></td>
</tr>
<tr>
<td><strong>Length of antithyroid treatment</strong></td>
<td>10-14 months</td>
<td>16-20 months</td>
<td></td>
</tr>
<tr>
<td><strong>Type of treatment</strong></td>
<td>Antithyroid drugs</td>
<td>Antithyroid drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnose</strong></td>
<td>Grave’s Disease *</td>
<td>Grave’s Disease *</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>matched 1:1 to Group I</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Verified by criteria and physician.

In the same way patients who were visiting the Department of Medicine with confirmed GD during the period 2012-07-01 to 2014-12-31 and treated with ATD for 16-20 months were identified. From these 62 patients a match was made towards each of the patients in GI. The
match was made by age. Consequently 36 patients were matched to this control group (GII) Figure 1 displays the age distribution for GI and the age matched GII.

![Figure 1. Age distribution for Group I and the age matched Group II.](image)

Following data was registered from the medical records: age, gender, smoking habits (smoker, non-smoker, former smoker), occurrence of eye symptoms (verified by ophthalmologist), treatment length, reported relapse of GD, TRAb levels at diagnosis and at withdrawal of ATD.

Statistics
Data was collected in a Microsoft Excel 365 sheet. Figures and tables were made using Excel. Statistical analysis was made with Pearson’s chi-square test and Mann-Whitney U test calculated with SPSS. A p-value less than 0.05 was considered as statistically significant.

Ethics
It is always important to ask oneself when dealing with the personal information of others, such as medical records, what is the purpose and does the purpose motivate this intrusion of integrity? The content of health records consists of personal information. Therefore, it is important that the records and the information they carry are handled with great care and respect. The patient’s integrity is of great interest both for the patient’s trust to the medical authorities and for researchers.

This study tries to evaluate the efficacy of a treatment given at the clinic and is a part of the clinic’s own quality control approved by the local head of department. Regarding projects
carried out by students and quality control projects there is, unless the results will be published as a journal article, no obligation for an ethics appeal at the Swedish Ethical Review Authority.

The list with personal code numbers and the key to the data chart serial number is stored in a sealed locker at the department. The data chart is saved at a password protected computer, available only to the writer of this article. The results are presented so that no individual can be identified. The risk that a patient will be identified is considered very low. This, and the knowledge this study may bring, motivates the integrity intrusion and the use of personal information for this study.

Results

Characteristics of the two groups are shown in table 2. In total the groups include 72 patients. Altogether, 17 patients experienced relapse of GD, eleven (30.6%) in GI and 6 (16.7%) in GII. The difference in relapse rate between the groups (GI and GII) was not statistically significant, p=0.165 calculated with a Pearson’s chi-square test.

Two patients in GI were treated with monotherapy and 34 with BR, in GII all patients received BR. Occurrence of ophthalmologist verified ophthalmopathy was three cases in total. Among patients in GI there was missing information about smoking habits in five cases and in one case TRAb level data was missing. None of the differences in the group characteristics regarding gender, eye symptoms and smoking habits were statistically significant.

Table 2. Characteristics for Group I (twelve months anti-thyroid drug treatment) and Group II 18 months treatment. SD=standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=36)</th>
<th></th>
<th>Group II (n=36)</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quantity</td>
<td>Percentage</td>
<td>Quantity</td>
<td>Percentage</td>
<td></td>
</tr>
<tr>
<td>Mean treatment days</td>
<td>390.5 (35)</td>
<td>30.6%</td>
<td>573 (38)</td>
<td>16.7%</td>
<td>0.165</td>
</tr>
<tr>
<td>Relapse after 1.5 yrs</td>
<td>11</td>
<td>30.6%</td>
<td>6</td>
<td>16.7%</td>
<td></td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>6</td>
<td>16.7%</td>
<td>5</td>
<td>13.9%</td>
<td>0.743</td>
</tr>
<tr>
<td>female</td>
<td>30</td>
<td>83.3%</td>
<td>31</td>
<td>86.1%</td>
<td></td>
</tr>
<tr>
<td>Smokers:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current+former</td>
<td>12</td>
<td>33.3%</td>
<td>10</td>
<td>27.8%</td>
<td>0.938</td>
</tr>
<tr>
<td>Former</td>
<td>4</td>
<td>11.1%</td>
<td>5</td>
<td>13.9%</td>
<td></td>
</tr>
<tr>
<td>No report</td>
<td>5</td>
<td>13.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine ophthalmopathy</td>
<td>1</td>
<td>2.8%</td>
<td>2</td>
<td>5.6%</td>
<td>0.555</td>
</tr>
</tbody>
</table>
Median TRAb levels for GI was 3.2 units/litre (E/L) and corresponding level for GII 4.95 E/L. The difference in TRAb levels was revealed statistically significant by a Mann-Whitney U test, calculated p-value 0.015. TRAb levels at diagnosis for Group I and II are illustrated in figure 2.

At the end of the study period 25 (69.4%) of the patients in GI and 30 (83.3%) of GII remained in remission. The last patient to relapse did so after 491 days. Figure 3 displays the relapses in relation to the follow up time. In GI four patients relapsed during the first six months after withdrawal of ATD, in GII the corresponding number was three.
Discussion

This study indicates that there are higher relapse rates in patients treated with ATD for twelve months compared to a longer 18-month therapy. A previous study from Allanic et al. [25] found that patients treated with ATD for 18 months relapsed in 38.2% of cases compared to a six month regimen where 58.3% relapsed. Abraham et al. [28] argue that there is a statistically significant advantage to treat GD with ATD for twelve to 18 months compared to six months. But whether 12 months ATD treatment is as good as 18 months is not known. Since there are side effects of ATD that can cause severe injury and inconvenience for the patients, it is of great interest to treat GD with ATD for as short time as possible. This study did not reach statistically significant difference, but the indication is important to follow up with other studies.

The retrospective design of this study did not, like previous studies, allow the possibility to actively follow the patients beyond the regular routines of the clinic, for example extra laboratory tests and physical examinations [26,29]. The Department of Medicine in Örebro follow all their GD patients with a doctor’s appointment three months after ATD withdrawal as standard and thereafter follow up is dependent on patient status. This study relies on that patients who experience relapse attend the same clinic for further treatment of their GD, which is normally the case, but we cannot preclude some cases might be missing. Until today it has not been possible to achieve a more extended follow up time in patients with the new twelve months ATD regimen. The chosen time for follow up of 1.5 years does not allow recognition of patients who experience relapse late and it also limits the size of the intervention group, since the change of regimen is fairly new. It is known that relapse can occur decades after the first episode of GD [19]. On the other hand, the highest risk of relapse lies within the 1.5 years of follow up.

Smoking is a known risk factor for relapse of GD as Hoermann et al. [29] showed in their study. In this study no statistically significant difference could be shown between the groups. The same situation is valid for gender distribution between GI and GII. The groups are matched by age to avoid effect of the fact that younger age is a risk factor for relapse [12]. Altogether these circumstances and that the differences between the groups are not significant, support the strength of this study since the groups are equal considering these factors.

In contrast, TRAb levels were statistically significantly higher in GII (median 4.95 E/L) compared to GI (median 3.20 E/L). According to previous research higher TRAb levels can
be used as a prediction of relapse on group level but not in single cases [13]. In this study, the GII-group had a lower number of relapses one could argue that this risk factor did not influence the results. On the other hand, it might indicate that the 18-month ATD regimen is more efficient considering relapse rate of GD due to the observation that TRAb levels on group level predict increased risk of relapse.

Because of the short retrospective perspective less patients than hoped for were included, making the available study groups small, limiting the statistical power of this study. It is however considered of importance to depict a preliminary picture of the results of a new ATD regimen. Information about patients excluded, based on longer than the planned twelve-month ATD regimen, was not collected. That information would have been valuable when the results were analysed. The measure of endocrine ophthalmopathy is in part uncertain as it was sometimes difficult to reach the ophthalmologist opinion through medical records. The time span in the inclusion criteria are relatively wide. The extremes 14 months ATD in GI compared to 16 months in GII is closer in time than the span within each group.

All patients included in this study were diagnosed and treated at the same medical department at the same hospital. There is a standardised routine for ATD treatment of GD, and has been for the whole period of time that this study comprises, which contributes to an equivalent assessment of the patients regardless of who the examining physician is. The group of physicians has been quite stable during the period of the study. This is important as the diagnosis of GD is dependent on several variables [7]. Furthermore, patient TSH and TRAb test have been analysed at the same laboratory. Finally, all medical records have been reviewed by the same reviewer. All these prerequisites make comparison of our two patient groups beneficial.

Analysing the result we realised that it ought to be interesting to follow up patients that got their planned treatment with ATD prolonged or switched to other types of treatments for different reasons. Because we have no reliable measure to predict which patients are at greatest risk of relapsing GD [13] that information would be valuable for further research. This study indicates that there is a difference between twelve and 18 months of ATD that needs to be evaluated in further studies. To find convincing evidence of which treatment duration to prefer, longer studies including a greater number of patients need to be performed.

Most of the patients in this study received BR therapy, according to the treatment tradition at the hospital. A study by Renwein et al. [30] state that there is no difference between a high (40 mg) dose of methiamazole and a low (10 mg) dose regarding relapse rate of GD.
Hence, there have been several studies trying to figure out the optimal ATD therapy duration [28]. A maybe more relevant subject to explore would be to find reliable factors predicting which patients that will benefit from a shorter ATD regimen.

**Conclusion**

According to the results, this study indicates that; to minimise the risk of relapsing GD, patients treated with ATD could benefit from an 18-month regimen rather than twelve months. But the difference was not statistically significant. Hence, the question of this study needs to be evaluated further by larger scale studies, to find convincing evidence.
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