Advances in Obesity, Endocrinology, and Diabetes

Volume 1 Issue 1 (July-Dec 2024) | **ISSN**: 3049-0715

"Identifying Key Predictors of Long-term Remission in Graves' Disease After Antithyroid Drug Treatment

Yosra Hasni 1,3 y.hasni@gmail.com Sondes Chermitti 2,3 Hamza EL FEKIH 1,3 Imen HALLOUL 1,3 Ghada Saad 1,3 Wided DEBBABI 2,3

1 Endocrinology-Diabetology Department, CHU Farhat Hached of Sousse, 4000 Sousse, Tunisia

2 Endocrinology Department, CHU Ibn Jazzar, 3199 Kairouan, Tunisia

3. Faculty of Medicine of Sousse, 4023 Sousse, University of Sousse, Tunisia

Abstract

Introduction:

Treatment of Graves' disease (GD) is based on the triad of antithyroid drugs (ATD), radioactive iodine and surgery (total or subtotal thyroidectomy).

ATD remains the first-line treatment.

Aim: to determine predictors of GD remission after treatment with ATD.

Methods: Cross-sectional study for analytical purposes including 105 patients followed for GD treated with ATD for 12 to 18 months. The collection of clinical and biological data was done through the consultation of medical records. Patients were divided to two groups according to their outcome. The "Remission" group included patients with durable euthyroidism after treatment withdrawal. The "Failure" group included patients who did not achieve euthyroidism at the end of treatment or who had relapsed after treatment withdrawal. Results were compared using Chi-Square test and t-test and logistic regression model with significance at $p < 0.05$.

Results: Patients in the "Remission" group were 43 (40.95%) and patients in the "Failure" group were 62 (59.05%). Factors that were significantly associated with remission at univariate analysis were: a shorter duration of symptom progression, a shorter duration of treatment, a lower initial anti-TSH receptor antibodies level, methimazole use compared to Benzylthiouracil use and better therapeutic adherence. Multivariate analysis showed that only shorter treatment duration ($p = 0.01$, OR = 0.90, IC95% [0.87 0.97]), lower initial anti-TSH receptor antibodies level ($p = 0.016$; = 0.93, IC95% [0.87-0.98]) and methimazole use ($p = 0.048$, OR = 2.4, IC95% [1.00-5.74]) were significant predictors of remission.

Conclusion: A lower initial level of anti-TSH receptor antibodies, the use of methimazole compared to Benzylthiouracil as well as a shorter duration of treatment are factors of better prognosis in the outcome of Graves' disease after Antithyroid drug treatment.

Key-words: Graves' disease – Antithyroid drugs – remission

List of Abbreviations

GD: Graves' disease

Volume 1 Issue 1 (July-Dec 2024) | **ISSN**: 3049-0715

ATD: antithyroid drugs
TRAbs: TSH receptor antibodies
BTU: Benzylthiouracil
MMI: Methimazole

INTRODUCTION

Graves' disease (GD) is an organ-specific autoimmune disorder characterized by the stimulating effect of circulating TSH receptor antibodies (TRAbs) (1). The activation of these receptors leads to hyperplasia of follicular cells, resulting in goiter and excessive production of thyroid hormones (2). Antithyroid drugs (ATDs) are the first-line treatment for most cases of hyperthyroidism associated with GD (3, 4). However, a significant drawback of this treatment is the high rate of treatment failure and relapse, with reported rates of sustained remission varying widely, not exceeding 70% (5). This variability suggests that certain factors may play a role in predicting treatment response. Identifying these factors could help in recognizing patients who are more likely to experience unsuccessful outcomes and may require more aggressive treatment strategies. In Tunisia, where ATDs are commonly prescribed for hyperthyroidism related to GD, there is a lack of recent studies assessing factors influencing the course of GD following ATD treatment in the local population. Therefore, we conducted this study to determine the predictive factors for remission in patients with Graves' disease treated with ATDs.

PATIENTS AND METHODS

This study is a retrospective observational analysis conducted at the Endocrinology-Diabetology department of Farhat Hached University Hospital in Sousse, Tunisia. We collected data from patients diagnosed with GD who were followed in the department over a six-year period, from January 2010 to December 2015.

Inclusion Criteria

- Patients diagnosed with GD and initially followed in the department.
- Patients whose initial treatment choice was medical therapy with ATDs: Benzylthiouracil (BTU) or Methimazole (MMI).
- Patients with a minimum follow-up of 24 months.
- Patients treated with ATDs for 12 to 18 months.

Data regarding patients and their disease were collected from medical records using a pre-established data collection form.

Group Classification

Patients were divided into two groups based on their clinical outcomes:

- **Remission Group**: Patients who achieved sustained euthyroidism after discontinuation of treatment.

Volume 1 Issue 1 (July-Dec 2024) | **ISSN**: 3049-0715

- **Failure Group**: Patients who did not achieve euthyroidism by the end of treatment or who experienced a relapse after treatment cessation.

Definitions of Variables

- **Remission**: Achieving biochemical euthyroidism that lasts for at least 3 months after stopping ATDs . Biochemical euthyroidism is defined as a normal TSH level (between 0.25 and 4.5 mUI/L) along with a normal FT4 level (between 7 pg/ml and 19 pg/ml) (6).
- **Relapse**: Recurrence of biochemical hyperthyroidism within one year following the cessation of ATD treatment. Biochemical hyperthyroidism is defined as a TSH level below 0.25 mUI/L with either a normal FT4 level (subclinical hyperthyroidism) or an elevated FT4 level above 19 pg/ml (overt hyperthyroidism) (7).
- **Failure**: The absence of remission.

Data collected were entered and analyzed using SPSS 20 software. For comparisons of independent series, we used the Pearson $\chi 2$ test for percentages and the Student t-test for means. Statistical significance was defined by a p-value < 0.05 and a 95% confidence interval.

RESULTS :

A total of 105 patients (69 women and 36 men) met the inclusion criteria.

Their clinico-biological characteristics are summarised in Table 1.

The "Remission" group included 43 patients and the "Failure" group included 62 patients. The remission rate was 41% and the failure rate was 59%.

The factors associated with remission in the univariate analysis were a shorter duration of symptom progression, a longer duration of treatment, and a longer duration of treatment, lower levels of antiTSH receptor antibodies (TRAbs), treatment with MMI versus treatment with BTU, and better therapeutic adherence (Table 2).

A multiple binary logistic regression analysis was performed to determine independent prognostic parameters for progression to remission after medical treatment with ATD. The analysis revealed that the type of ATD prescribed was one of the factors influencing the course of GD. Treatment with is therefore a predictive factor for remission of the disease (p=0.048) with OR=2.40 [95% CI [1.00 - 5.74]. Other factors were identified as being predictive of remission of GD under medical treatment with treatment, such as the initial level of TRAbs and the duration of treatment with ATD. Indeed, a low initial TRAbs level and a short duration of ATD treatment were predictive of remission (table 3).

DISCUSSION

The identification of prognostic factors for the evolution of GD after medical treatment with ATD would be particularly useful in identifying those patients who are most likely to fail to respond to the

treatment and who should therefore be treated more aggressively from the outset (8). Several studies have interested in determining these factors in different populations. Ross et al (4) reported that patients with GD, are more likely to respond to ATD are those who are female, aged over 40, with moderate hyperthyroidism, a small goitre and negative or low titer TRAbs.

In our experience, remission of GD was unsatisfactory, with only 41% of our patients achieving remission after stopping medical treatment. This confirms the relatively low remission rates reported in several studies (10). However, according to the latest recommendations of the majority of learned societies, ATDs are the first-line treatment indicated for the treatment of GD related hyperthyroidism (9,11,12).

In a review of the literature, Piantanida et al (8) analysed the various factors that may be involved in the development of GD after medical treatment. They concluded that the role of age, gender and the severity of hyperthyroidism remains uncertain. On the other hand, they reported that the role of Graves' orbitopathy and smoking are possible, while the role of thyroid volume and persistence of TRAbs at the end of treatment. On the other hand, in an earlier retrospective study published by Allahabadia et al (13) including 536 patients, it was reported that age over 40 years ($p=0.01$) and female gender ($p<0.001$) were predictive of remission of GD.

Another study including 218 patients with GD published by Magri et al. in 2016 confirmed the association with a better prognosis of GD treated with ATD ($p=0.03$) (14). In our study, age, intoxication, presence of a family history of dysthyroidism, exophthalmos, severity of hyperthyroidism and thyroid volume did not differ significantly between the "Remission" group and the "Failure" group.

However, a shorter duration of symptom evolution ($p=0.02$), use of MMI ($p=0.012$), shorter duration of treatment ($p=0.001$), better therapeutic adherence ($p=0.018$) and a lower initial TRAbs rate ($p=0.006$) were significantly associated with remission in the univariate analysis.

After binary logistic regression of the different variables, only the lower initial level of TRAbs ($p=0.016$; OR=0.93; IC95%[0.87-0.98]), the use of MMI ($p=0.048$;OR=2.4; IC95%[1.00-5.74]), and the shorter duration of treatment were significantly associated with remission ($p=0.01$; OR=0.90 ; IC95%[0.87-0.97]).

Nonetheless, the weak predictive power of a single risk factor remains insufficient to predict a patient's outcome.

Recently, Vos et al (15) developed the GREAT (Graves' Recurrent Events AfterTherapy) score, based on goitre volume assessed by palpation, fT4 and TRAbs levels and age at the time of diagnosis, which can be used to predict the risk of MB recurrence before initiating treatment. Later, Bartalena et al (16) developed another predictive score called the Clinical Severity Score (CSS) based on the Merseburg triad (goitre, hyperthyroidism and exophthalmos). A study which

evaluated and compared these two scores and concluded that the CSS and GREAT scores are useful tools for predict the possibility of hyperthyroidism relapse after treatment (17).

Conclusion

It would be interesting to study the factors predictive of remission under treatment with TSA in large national studies. It could help to identify patients who are less likely to respond to medical treatment, in whom radical treatment could be proposed from the outset. In this way predictive scores of remission under ATD, adapted to our Tunisian context, could also be established to help in the therapeutic decision.

References

1. Ross DS et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016 Oct;26(10):1343-1421. doi: 10.1089/thy.2016.
2. Testa RM, Martinelli S, Pacini F. Diagnosis and Treatment of Hyperthyroidism. Clin Appl Nucl Med . 2018. 3-17.
3. Chung JH. Antithyroid Drug Treatment in Graves' Disease. Endocrinol Metab (Seoul). 2021 Jun;36(3):491-499. doi: 10.3803/EnM.2021.1070. Epub 2021 Jun 16
4. Kim HJ. Long-term management of Graves disease: a narrative review. J Yeungnam Med Sci. 2023 Jan;40(1):12-22. doi: 10.12701/jyms.2022.00444. Epub 2022 Nov 4.
5. lfadda A, Malabu UH, El-Desouki MI, Al-Rubeaan KA, Al-Ruhaily AD, Fouda MA, et al. Treatment of Graves' hyperthyroidism--prognostic factors for outcome. Saudi Med J. 2007;28:225 30.
6. Jin M, Jang A, Kim CA, Kim TY, Kim WB, Shong YK, Jeon MJ, Kim WG. Long-term follow-up result of antithyroid drug treatment of Graves' hyperthyroidism in a large cohort. Eur Thyroid J. 2023 Mar 17;12(2):e220226. doi: 10.1530/ETJ-22-0226
7. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Heterogenous biochemical expression of hormone activity in subclinical/overt hyperthyroidism and exogenous thyrotoxicosis. J Clin Transl Endocrinol. 2020 Feb 8;19:100219. doi: 10.1016/j.jcte.2020.100219
8. Piantanida E, Lai A, Sassi L, Gallo D, Spreafico E, Tanda M, et al. Outcome prediction of treatment of Graves' hyperthyroidism with antithyroid drugs. Horm Metab Res. 2015;47:767-72.
9. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26:1343-421.
10. Nedrebo B, Holm PI, Uhlving S, Sorheim J, Skeie S, Eide GE, et al. Predictors of outcome and comparison of different drug regimens for the prevention of relapse in patients with Graves' disease. Eur J Endocrinol. 2002;147:583-9.
11. Lane LC, Cheetham T. Graves' disease: developments in first-line antithyroid drugs in the young. Expert Rev Endocrinol Metab. 2020 Mar;15(2):59-69. doi: 10.1080/17446651.2020.1735359

Volume 1 Issue 1 (July-Dec 2024) | **ISSN**: 3049-0715

12. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018;7:1 20.
13. Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SC, Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. J Clin Endocrinol Metab. 2000;85:1038-42.
14. Magri F, Zerbini F, Gaiti M, Capelli V, Ragni A, Rotondi M et al. Gender influences the clinical presentation and long-term outcome of graves disease. Endocr Pract. 2016;22:1336-42.
15. Vos XG, Endert E, Zwinderman A, Tijssen JG, Wiersinga WM. Predicting the risk of recurrence before the start of antithyroid drug therapy in patients with Graves' hyperthyroidism. J Clin Endocrinol Metab. 2016;101:1381-9.
16. Bartalena L, Masiello E, Magri F, Veronesi G, Bianconi E, Zerbini F et al. The phenotype of newly diagnosed Graves' disease in Italy in recent years is milder than in the past: results of a large observational longitudinal study. J Endocrinol invest. 2016;39(12):1445-51.
17. Masiello E, Veronesi G, Gallo D, Premoli P, Bianconi E, Rosetti S et al. Antithyroid drug treatment for Graves' disease: baseline predictive models of relapse after treatment for a patient-tailored management. J Endocrinol Invest. 2018;41(12):1425-32.