Original Article

Outcome of Graves ' disease after Anti-thyroid Drug treatment in South West of Iran

Hajieh Shahbazian[1], Saied Saiedinia[2], Armaghan Moravej Aleali[3]

ABSTRACT

***Objective*:** This study was conducted to observe the optimal results of long term treatment with antithyroid drugs in patients with graves´ disease.

***Methodology*:** Total of 268 patients with graves´ disease who were referred to endocrinology clinic during 2005 – 2008 and treated with anti-thyroid drugs for a long term were studied. Data about the age, gender, estimated weight of thyroid before and after the treatment, level of thyroid hormones, disease relapse, hypothyroidism and the drug side-effects were collected and analyzed.

***Results*:** Eighty two (31%) patients were males, 186 (69%) females, mean age of 35±27 years and follow-up course of 31±16 months], were studied. After the discontinuation of long term treatment, 53% were affected with relapse of hyperthyroidism. The mean duration of hyperthyroidism relapse after the treatment was 8.3±7.3 months. The relapse rate was significantly higher in the treated patients in both ends of age spectrum (P < 0.001). In males and patients with large thyroid and lower TSH level at the end of treatment, the rate of relapse was higher (P=0.016, P < 0.033, P=0.001 respectively). The incidence of hypothyroidism after treatment was about 6%. More decrease of thyroid size during the treatment course, higher level of serum TSH after discontinuation of the treatment, and lower thyroid hormone levels before the treatment were some of the effective factors in hypothyroidism incidence (P=0.005, P<0.001, P < 0.05 respectively). Of the 268 graves´ patients treated with antithyroid drugs, 104 patients (39%) remained euthyroid in the follow-up course.

***Conclusion*:** Using long-term treatment with antithyroid drugs is still the first step in treating patients with graves´ especially in middle-aged women with smaller goiters.

KEYWORDS: Anti-thyroid drug, Hyperthyroidism, Graves' disease, Hypothyroidism, Methimazole, Propyl-Thiouracil.

Pak J Med Sci April - June 2012 Vol. 28 No. 3 445-449

How to cite this article:

Shahbazian H, Saiedinia S, Aleali AM. Outcome of Graves' disease after Anti-thyroid Drug Treatment in South West of Iran. Pak J Med Sci 2012;28(3):445-449

1. Hajieh Shahbazian,
Endocrinologist, Associated Professor,
Head of Diabetes Research Center,
2. Saied Saiedinia,
General Practitioner,
3. Armaghan Moravej Aleali,
General Practitioner,
1-3: Diabetes Research Center,
Ahvaz Jundishapur University of Medical Sciences,
Post Code: 61357-15794, Ahvaz, Iran.

Correspondence:

Armaghan Moravej Aleali,
E-mail: armaghanaleali@yahoo.com

* Received for Publication: September 5, 2011
* 1st Revision Received: October 10, 2011
* 2nd Revision Received: January 2, 2012
* Final Revision Accepted: January 20, 2012

INTRODUCTION

Graves´ disease (GD) is one of the prevalent autoimmune diseases and the most common cause of hyperthyroidism all over the world with the incidence of 60-80% of ***thyrotoxicosis*** cases.[1] Although some trivial cases of GD may recover automatically, in most cases the clinical symptoms of the disease would become more critical without any major treatment.[1]

The mortality rate of 20-30% due to GD was reported before using adequate treatments.[1] In addition, the incidence of some deleterious side-effects like ophthalmopathy, cardiovascular signs

and symptoms such as agitation, gastrointestinal symptoms, menstrual disorders, myopathy and weight loss indicate the necessity of urgent and adequate treatment.[1,2]

The treatment of hyperthyroidism due to GD is performed by decreasing thyroid hormone synthesis by using anti-thyroid drugs or decreasing thyroid tissue using radioactive iodine treatment (^{13}I) or surgical ablation. Selecting the proper method of treatment still remains controversial. The most frequent method of treatment in many therapeutic centers in Europe and Japan is administration of anti-thyroid drugs, while in North America radioactive iodine treatment is the first-line of therapy. These differences indicate that none of these therapeutic methods is completely adequate, and those patients may need different therapeutic methods.[1,3]

This study was conducted to observe the optimal results of long term treatment with anti-thyroid drugs in patients with graves´ disease and evaluate the factors that affect the relapse of hyperthyroidism and incidence of hypothyroidism after discontinuation of the treatment.

METHODOLOGY

This cross-sectional study was done on 268 patients with graves´ diseases who were referred to Ahvaz Golestan hospital endocrine clinic during 2005 – 2008 and were treated by long term anti-thyroid drugs administration. Patients who did not complete the follow-up course were excluded, and those who had relapse of hyperthyroidism after discontinuation of long-term treatment, or do not complete long-term treatment due to lack of response to treatment and were treated with other methods (radioactive iodine, surgery) were considered as the relapsed cases. All the patients were checked and followed up by an endocrinologist. A questionnaire including age, gender, beginning time of treatment, duration of treatment, the consumed anti-thyroid drug, estimated weight of thyroid, the relapse of disease during the treatment or after the completion of it, the incidence of hypothyroidism after the completion of long-term treatment with drug, serum TSH, T3, T4, levels and T3RU at the beginning and the end of treatment and the duration of follow-up course, was completed for each patients.

Hyperthyrodism was defined by T4>upper limit of normal rang (12.5µg/dl) and TSH<0.1MIU/L and FTI>4.6, hypothyroidism by TSH>upper limit of normal range (4MIU/L) with or without T4<4.8 µg/dl (in clinical and subclinical hypothyroidism respectively) and Euthyroidism by normal range T4(4.8-12.5 µg/dl)FTI(1.2-4.6) and TSH(0.3-4 MIU/L). The ethical review board of Ahvaz Jundishapur University of Medical Sciences has approved the study proposal and informed consent was obtained from all subjects. SPSS version 14 was used for data collection and chi square test and ANOVA used for analysis. P value less than 0.05 was considered as significant.

RESULTS

Total of 268 patients 82 (31%) males, 186 (69%) females mean age 35±27 years and follow–up course of 31±16 months, were studied. Among them, 28 patients (10.5%) received propyl-thiouracil (PTU) and 240 (89.5%) received methimazole (MTZ). The mean duration of drug consumption in the patients was 19±5 months. The patients were followed up with the average time of 31±16 month after the discontinuation of drug therapy.

Relapse of hyperthyroidism was seen in 98 patients (37%) after discontinuation of long term treatment. Fifty patients (19%) relapsed during the long term treatment with antithyroid drugs by decreasing the dose of drug. A total of 148 patients (55%) with graves´ disease who were treated with long term consumption of antithyroid drugs were affected with the relapse. The mean incidence time of relapse of hyperthyroidism after the completion of long-term treatment with anti-thyroid drugs was 8.3±7.3 months. (Table-I)

The mean age of patients with the relapse of hyperthyroidism was 39±5 years, which_showed no statistical significant difference with the patients who were not affected with relapse (39 ± 5 years vs. 31±11 years) (P<0.069). However, the relapse of hyperthyroidism was higher in both ends of age spectrum (P<0.001) Patients under 10 years

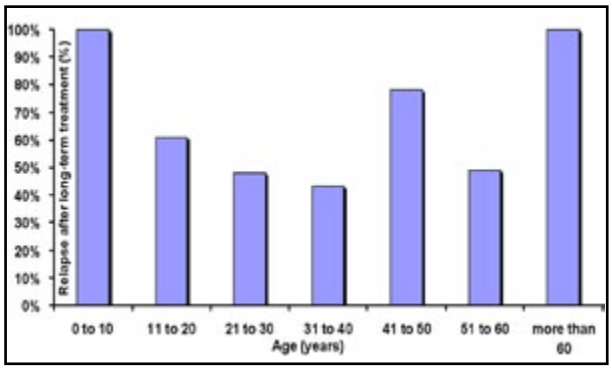

Fig.1: The rate of the relapse of hyperthyroidism after long-term treatment with antithyroid drugs in different age groups.

Table-I: The rate of the relapse in different times of follow-up course after the end of drug treatment.

No. of cases	*Time (months)*	*Cumulative Percentage*	*Percentage*
52	6	53.1%	53.1%
30	6 to 12	83.7%	30.6%
14	12 to 24	98.0%	14.3%
2	After 24	100	2.0%
98	Sum	-	100%

of age and above 60 years almost always relapsed after discontinuation of treatment. The least relapse rate (45%) was observed in 31-40 years old patients (Fig.1). 52 out of 82 men (63%) and 89 out of 186 women (48%) showed relapse. These results showed that the relapse rate was higher in men than the women (P=0.016).

The rate of relapse of hyperthyroidism in patients consuming PTU (propyl-thiouracil) was 64% (18 out of 28 patients) and for patients consuming methimazole was 52% (124 out of 240) which was not statistically significant (P=0.143). The mean duration of drug consumption in relapsed patients was 19±6 months, and in non relapsed patients was 18±4 months that showed no significant difference. The weight of thyroid according to the estimation by palpation before and after long term treatment with antithyroid drugs was significantly higher in relapsed than non relapsed patients (39±10 gram vs. 36±9 gram before treatment and 38±9 gram vs. 32±8 gram after treatment in relapsed and non relapsed patients) (P=0.033 and P<0.001, respectively).

The level of serum T4 and FT4I before treatment in patients with the relapse of hyperthyroidism showed no significant difference with the nonrelapsed patients, but the level of serum T3 and T3RU before treatment was significantly higher in relapsed patients (P=0.045, P=0.019 respectively) (Table-II). Moreover, after the completion of treatment, serum TSH level in relapsed patients was significantly lower than non relapsed patients (P=0.001).

Among the treated patients, 16 patients (6%) were affected with hypothyroidism after the completion of treatment. The mean duration of hypothyroidism incidence was 13.4±13.8 months after the discontinuation of long term treatment with anti-thyroid drugs. Many factors were evaluated in hypothyroid and euthyroid patients (Table-III).The mean age of the patients with or without hypothyroidism showed no statistical significant difference (P=0.192). The incidence rate of hypothyroidism was not different in men and women. (P=0.425).

Type and duration of antithyroid drugs consumed by patients showed no significant effect on incidence of hypothyroidism. (P=0.515 and P=0.314 respectively)

The size of thyroid did not differ significantly between both groups (hypothyroid and euthyroid) before and after treatment with anti-thyroid drugs. However among patients with hypothyroidism the decrease of thyroid weight (estimated by palpation) was significantly higher during the treatment course (P=0.005). After the end of treatment, serum TSH level in hypothyroid group was significantly higher than euthyroid group (P<0.001). Lower basal (before treatment) FTI and T3RU were detected in hypothyroid patients comparing with euothyroid cases (P=0.005, P= 009)

The total incidence rate of side-effects resulting from the long term use of anti-thyroid drugs was 10% (26 patients from a total of 268). Of them, 10 patients (4%) were affected with itching and skin reactions, 8 patients (3%) with a trivial decrease in WBC count (granolocytopenia), 4 patients (1.5%) with arthralgia and 4 patients (1.5%) with hepatitis. All of these side-effects resulted from the use of methimazole, and no case of agranulocytosis and lupus like syndrome was observed. From the total of 268 patients with graves´ disease, treated with anti-thyroid drugs, 104 patients (39%) remained euthyroid in follow-up course of 31±16 months.

Table-II: The mean serum level of thyroid hormones at the beginning of disease and TSH after the completion of treatment in patients with the relapse of hyperthyroidism and euthyroid patients.

Serum level of hormones	*Patients with the relapse of hyperthyroidism*	*Euthyroid patients during follow-up course*	*P-value*
T4 mg/dl	17±6	20±27	P=0.206
%FTI	9±4	9±4	P=0.371
T3 ng/ml	370±188	328±152	P=0.045
%T3RU	41±8	38±9	P=0.019
Serum level of TSH after treatment MIU/ml	0.6±0.5	1.6±1.2	P=0.001

DISCUSSION

The long-term treatment with anti-thyroid drugs is usually the primary method of treatment in patients with recently diagnosed graves´ disease.[4] The rate of relapse after the treatment in our study was 55% in 31±16 months of follow up. In a similar study performed by Wille et al (2006) on graves´ patients treated with anti-thyroid drugs, from the total of 76 patients who were followed up for 99±22 months, 42 patients (70%) were relapsed.[4] In a study by Leary et al, the rate of relapse after the mentioned treatment was 68%, and in two other studies it was 60%.[5-7] Rate of relapse was 82.5 in Bolanos study.[8]

In another study which was carried on in Iran by Heidari et al on 54 patients with graves´ the rate of relapse was 43%.[9] In total, the rate of relapse in these studies was different, and the differences were mainly due to the different duration of follow-up and the number of studied patients. It seems that the degree of improvement is not the same in different geographical areas.[1] In our study and Heidari et al in Iran the relapse rate was lower than the other countries.

In this study the mean time of relapse after the end of treatment with anti-thyroid drugs was 8.3±7.3 months. The mean time in other similar studies was 8.2±14.5 months.[7,8,10,11]

The majority of relapse was in the first 6 months after the end of treatment (53%), and about 84% of patients relapsed during the first year after the discontinuation of long term treatment with anti-thyroid drugs, which indicates the necessity of close follow-up in this time period. It's not easy to anticipate which patients will relapse after long term treatment with anti-thyroid drugs, but the results of this study showed that the rate of relapse was higher in men and patients who had bigger goiter size before and after the treatment with anti-thyroid drugs.

If thyroid showed more decrement in size during treatment course, and more increment in serum TSH level, the chance of a further relapse will decrease. Although the mean age of the patients and the mean duration of drug consumption in patients with relapse were higher, the difference was not statistically significant. Nevertheless, the rate of relapse in both ends of age spectrum was very high. Patients under 10 years old and above 60 years old almost always relapsed after discontinuation of treatment .The least rate of relapse (45%) was observed in 31-40 years old patients**.** High serum T3 and T3RU before treatment and lower TSH at the end of treatment were significantly increased the relapse rate.

Table-III: Factors affecting incidence of hypothyroidism after discontinuation of treatment.

Factors		*P- Value*
Mean age of patients	Year	
Hypothyroidism	23±7	P=0.192
Euthyroid	36±39	
Sex		
Men	5%	P=0.425
Women	7%	
Hypothyroid in different drug user	No (%)	
PTU	2(7)	P=0.515
Methimazol	14(5)	
Mean duration of antithyroid consumption		
Months		
Hypothyroidism	17±2	P=0.314
Euthyroid	19±5	
Estimate weight of thyroid	Gram	
Before treatment		
Hypothyroid	37±9	P=0.812
Euthyroid	36±9	
After treatment		
Hypothyroid	31±7	P=0.102
Euthyroid	32±8	
decrement of thyroid size during treatment		
Hypothyroid	5/6±4	P=0.005
Euthyroid	2/4±4/5	
TSH level in the end of treatment	MUI/L	
Hypothyroid	8/3±17	P<0.001
Euthyroid	1/6±1/2	
Serum thyroid hormones level before treatment		
Total T4	µg/dl	
Hypothyroid	14/1±5/2	P=0.418
Euthyroid	18±19/7	
Total T3	ηg/dl	
Hypothyroid	267±134	P=0.048
Euthyroid	355±173	
T3Ru	%	
Hypothyroid	34±4/1	P=0.009
Euthyroid	40±9	
FTI		
Hypothyroid	6/4±3/2	P=0.005
Euthyroid	9/3±3/9	

Incidence of hypothyroidism after discontinuation of long term treatment with anti-thyroid drugs in this study was about 6% (1.7-4% in other studies).[4,5] Age, gender, type of drug and thyroid size before and after treatment with anti-thyroid drugs did not affect the rate of hypothyroidism , while decrement of thyroid size during treatment was higher, serum TSH level after treatment was higher, and thyroid

hormone levels before treatment were significantly lower than euthyroid patients. The mean incidence time of hypothyroidism was 13.4±13.8 months after the end of the treatment. The incidence of the major side-effects resulting from long term treatment with anti-thyroid drugs was very low (1.5% hepatitis and no case of agranulocytosis was observed). This problem resulted in discontinuation of drugs, but the trivial side-effects occurred in 8.5% of patients were treated with drug substitution and other supporting treatments. The incidence rate of side-effects in the previous studies has been reported as 1-5 %.[1]

Our patients were followed up for 31±18 months. They may experience relapse or hypothyroidism after this time course, therefore longer time follow up studies should be done to address this limitation.

Although the long term treatment with anti-thyroid drugs is still the first step in treating patients with GD there is no clear data about the duration of therapy necessary for the individual patient.[12] Some studies showed that treatment duration greater than 18 months did not improve remission rate.[13] Other studies conclude that long term (ten year) continuous treatment of hyperthyroidism with Methimazol is safe and complications and expense of treatment do not exceed those of radioactive Iodine therapy.[14] According to our study long term treatment with antithyroid drugs is better to be used in women or patients who do not have huge goiter at least for a course of 18-24 months. The smaller size of thyroid after the treatment and increased TSH levels at the end of treatment indicate that the patient can remain in an almost long term remission of thyrotoxicosis.

The use of this therapeutic method in patients under 10 and above 60 years old, male patients and those who have huge goiter will be accompanied by the high risk of hyperthyroidism relapse. Concerning the incidence of hypothyroidism and relapse of hyperthyroidism, recurrent follow-up is necessary during the first year, and afterward the intervals of follow-up will be longer.

ACKNOWLEDGEMENT

This paper is based on the thesis of Dr. Saied Saiedinia, and financial support was provided by Ahvaz Jundishapur University of Medical Sciences. (Reg.No.674).

REFERENCES

1. Jaueson JL, Weetman AP. Disorders of thyroid gland. In: Kasper DL, Braunwald E, Fausi IS, Hausser SL, Longo DL, Jaueson JL. Harisson's Principles of Internal Medicine. MC Graw –Hill. 16th edition. New York. 2005: 2104-2127.
2. Bonert V, Fried man TC. The thyroid Gland. In: Andreoli TE. Carpenter CCJ, Gnggs RC, loscalzo J. Cecil essentials of medicine. 6th edition. New York: Saunders. 2004: 593-602.
3. Lal G, Clarck OH. Thyroid, Parathyroid and Adrenal. In: Braundicendi FC, Anderson DK, Billiar TR, Dunn DL, Hunter GJ, Pollock Re. Schuuar TZ, Principles of surgery.8th edition. Newyork: MC Graw Hill. 2005: 1395-1429.
4. Wille T, Muller B, Both D, Burgi U, Diem P. Long-term follow up after anti thyroid drug treatment in Grave's disease. Praxis (Bern 1994) 2006;95(29-30):1121-1127.
5. Leary AC, Grealy G, Higgins TM, Buckley N, Barry DG, Murphy D, et al. Long-term outcomes of treatment of hyperthyroidism in Ireland. Ir J Med Sci 1999:168(1):47-59.
6. Hadj Ali I, Khiari K, Chérif L, Ben Abdallah N, Ben Maïz H, Hajri H, et al. Treatment of Graves' disease: 300 Case. Press Med 2004;33(1):17-21.
7. Wang PW, Liu RT, Tung SC, Chien WY, Lu YC, Chen CH. Outcome of Graves' disease after anti-thyroid drug treatment in Taiwan, J Formos Med Assoc 1998;97(9):619-25.
8. Bolanos F, Gonzalez-Ortiz M, Duron H, Sanchez C. Remission of Graves' hyperthyroidism treated with methimazole. Rev Invest Clin 2002;54(4):307-10.
9. Hedari B, Farhangi F, Amiri M. Comparison between anti-thyroid drug and radioiodine in thyrotoxicosis. Iranian J Endocrinology & Metabolism 2002;4(1):29-34.
10. Jonas M, Ambroziak U, Bednarczuk T, Nauman J. Predicting a relapse of Graves' hyperthyroidism in adults during the early phase of treatment with anti-thyroid drugs. Endokrynol Pol 2006;57(6):596-604.
11. Peixoto MC, Coeli CM, Vaisman M. Evaluation of the medical treatment of Graves' disease (GD). Arq Bars Endocrinol Metabol 2005;49(3):410-9.
12. Quadbeck B, Janssen OE, Mann K. Problems and new developments in the management of Graves' of disease: medical therapy. Z Arztl Fortbild Qualitatssich 2004;98(Suppl 5):37-4.
13. Maugendre D, Gatel A, Campion L, Massart C, Guilhem I, Lorcy Y, et al. Anti-thyroid drugs and Graves' disease: prospective randomized assessment of long term treatment. Clin Endocrinol (Oxf) 1999;50(1):127-32.
14. Azizi F, Ataie L, Hedayati M, Mehrabi Y, Sheihkoleslam F. Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioton. Eur J Endocrinol 2005;159(5):695-701.