ANTITHYROID DRUGS IN THE INITIAL MANAGEMENT OF GRAVES DISEASE: IDENTIFICATION OF CLINICAL AND THERAPEUTIC PROGNOSTIC FACTORS.

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BACKGROUND

Although antithyroid drugs are currently used as the primary treatment in Graves´ disease (GD), some questions relative to their use (good candidates, choice of drug, dosage, duration of treatment) remain unsolved. We review our experience in this field.

PATIENTS AND METHODS

We retrospectively reviewed the clinical records of an unselected sample of 65 patients with Graves´disease who attended our clinic between 1994 and 2004 and received antithyroid drugs as primary treatment. Graves´ disease diagnosis was established when autoantibodies against the TSH receptor, or an homogenous distribution of the radiotracer in the thyroid gland in a 99-Tc scanning or clinical signs of thyroid ophtalmopathy were present in a patient with hyperthyroidism They were followed for at least 12 months after antithyroid drug discontinuation. We registered patient characteristics, drug received and its dosage, months of treatment and length of follow-up.

RESULTS

Sex (female)	86,2 %
Age (mean ± SD)	39,5 ± 16,4
Tobacco smokers	13,6 %
Free T4	38±26 ng/L
Free T3	2,1±2,3 ng/L
Undetectable TSH	93,8%.
Positive TSI	34/41
Diffuse uptake in Tc99 scanning	35/36

Table 1. Baseline patients characteristics.

In a few patients levels of free hormones were not available: they had total T4 levels of 12,2±9,7 mcg/dl and total T3 of 2,0±2,24 ng/ml.

Drug	methimazole	19
	carbimazole	45
	propylthiouracile	1
Initial dose	methimazole	22,9±9,2 mg/day
	carbimazole	24±9,6 mg/day
	propylthiouracile	300 mg/day
Duration of treatment (median; IQR)		12 (10-18) months

Table 2. Treatment characteristics

Co-administration of tiroxine was indicated only in one patient.
Exanthema occurred in 3 patients (4,6%), but no severe adverse effects occurred.

FOLLOW-UP

A definitive treatment (131-I or surgery) was indicated in 9 patients after 12 – 34 months of treatment, when antithyroid drugs were considered ineffective. 27 patients (41,5%) were free of disease after a median follow-up of 23 months (IQR 17-36). The 38 persistences/recurrences were managed with a second course of antithyroid drugs (45,9%), 131-I (51,4%) or surgery (2,7%).

We could not find differences between patients who relapsed and those who did not in sex, age, tobacco consume or follow-up. Free T4 and T3 were similar in both groups, as is shown in table 3. Percentage of patients with positive TSI was similar, but TSI titers were significantly higher in patients who relapsed (p<0,05). The choice of metimazol or carbimazol did not correlate with the probability of relapse. Higher T4 levels showed a weak significant correlation with the initial dose (r=0,29 for free T4, r=0,64 for total T4, p<0,05), which was also correlated with the duration of treatment (r=0,39, p<0,01). Recurrence rates and disease free survival estimates were similar when comparing different dosages and durations of treatment (<12, 12-18, >18 months).

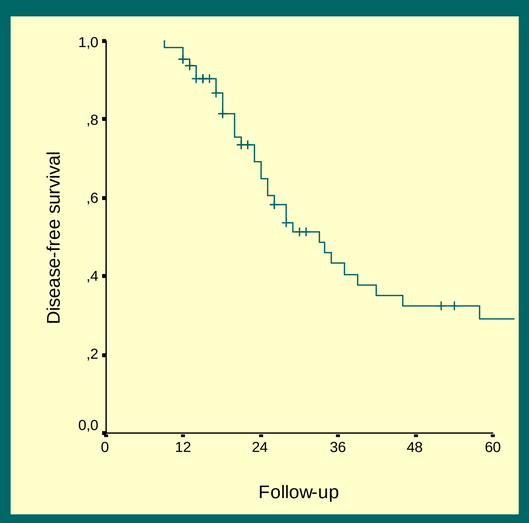

Figure 1. Kaplan-Meier estimates of disease free survival. Prognosis is worse than expected because we probably loose more patients with no recurrence during follow-up

	No recurrence	Recurrence	p value
Women/men	22/5	34/4	N.S.
Age	40,3+16,2	39+16,8	N.S.
Free T4	33,5+12,8	42,3+32,3	N.S.
Free T3	2,57+2,43	1,41+2,2	N.S.
Total T4	7,82+9,03	15,07+9,52	N.S.
Total T3	1,09+1,5	2,48+2,47	N.S.
Undetectable TSH	92,6%	94,7%	N.S.
Positive TSI	85%	81%	N.S.
TSI (U/ml)	6,88+6,03	25,08+32,15	P<0,05

Table 3. Clinical and biochemical presentation of patients who relapsed during follow-up and those who did not.

	No recurrence	Recurrence	p value
Metimazole/carbimazole/PTU (n)	8/19/0	11/26/1	N.S.
Dose (mg/day)	22,75+8,7	24,45+9,85	N.S.
Duration of treatment (months)	12,9+4,8	15+10,9	N.S.
Follow-up (months)	30,3+24,4	34,1+28,9	N.S.
Duration of treatment (months)	12 (10-14)	12 (8-18)	N.S.

Table 4. Treatment parameters in patients who relapsed during follow-up and those who did not.

CONCLUSIONS

It is difficult to identify patients that will not achieve a permanent remission of Graves´ disease with antithyroid drugs. The retrospective design of the study limited its value, since higher levels of T4 (and other clinical parameters not registered in the study) determined higher doses of antithyroid drugs and longer courses of treatment. High titers of thyroid-stimulating immunoglobulines predicted a worse prognosis. Longer courses of treatment or higher doses were not correlated with fewer recurrences. Prospective studies are needed to establish the optimal treatment schedule with antithyroid drugs for Graves´ disease.