Antithyroid drugs in Graves’ disease: Are we stretching it too far?

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ABSTRACT

Introduction: Early and durable achievement of euthyroid or hypothyroid status with low likelihood of relapse is the key to effective treatment of Graves’ disease (GD). Although antithyroid drugs (ATDs) are commonly used first-line agents, likelihood of remission remains highest with radioactive iodine (RAI) therapy and surgery. Data regarding efficacy and economical superiority of RAI therapy over ATDs are lacking from India. This study was designed to study the response to long-term (>12 months) use of ATDs in GD with respect to attainment of remission and to compare the cost of treatment with ATDs versus RAI therapy beyond 12 months. Settings: The study was conducted in a tertiary care center. Study Design: This was a retrospective analysis. Materials and Methods: Patients of GD in our follow-up from February 2009 to March 2016 who had received ATDs for a duration exceeding 12 months were retrospectively analyzed. Patients who underwent radioablation after a period of at least 12 months on ATDs were analyzed and their status was recorded after a minimum of 6 months after radioablation. Patients who remained hyperthyroid beyond 12 months and received RAI therapy were further compared with those who continued on ATDs, for achievement of euthyroid or hypothyroid status. Cost analysis was done for follow-ups and treatment and compared. Statistical Analysis Used: All analyses were done using Fisher’s exact test for categorical and descriptive statistics for numerical data. Results: Use of ATDs leading to euthyroid and hypothyroid status in GD patients was only significant beyond 24 years when compared to those at <12–18 months therapy (\(P = 0.0262\) and \(P = 0.0217\), respectively). The patients who ended up with hypothyroid status were significantly greater in RAI group compared to ATD group (\(P = 0.0003\)). Cost of therapy per patient beyond 12 months was lower in the RAI group compared to the ATD group (cost difference Rs. 5435.00). Conclusions: Within limitations, our study demonstrates that RAI is effective and economical option in GD.

Key words: Antithyroid drugs, cost, radioiodine therapy

INTRODUCTION

Early and durable achievement of euthyroid or hypothyroid status with low likelihood of relapse is the key to effective treatment of Graves’ disease (GD). Modalities of treatment of GD include antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, and surgery. ATDs are commonly used as the first-line therapy for a period that varies up to 12–18 months. Rate of remission is as low as 40–50% with ATDs and there are high rates of relapse among those who achieve remission on this mode of therapy.[1] Even with treatment with ATDs for 24 months, the rates of remission did not differ from those treated for 12 months only.[2] RAI therapy results in achievement of remission in 80–90% of patients and has low rates of relapse in GD.[3]
A meta-analysis of earlier studies has documented greater cost of therapy with RAI compared to ATDs although some studies have shown lesser cost with surgery and RAI when compared to ATDs. ATDs remain the mainstay of first-line therapy in our country and are often used for long periods. With increasing availability of RAI therapy, its documented safety, and reducing cost, there is a need to take a relook at our approach to management of GD. This study was designed with an aim to study the response to long-term (>12 months) use of ATDs in GD with respect to attainment of remission and to compare the cost of treatment of GD with ATDs versus RAI therapy in those requiring ATDs beyond 12 months.

**Materials and Methods**

This study was a retrospective data analysis of patients of GD in our follow-up during the period February 2009 to March 2016, who had received ATDs for a duration exceeding 12 months. The standard protocol at our center for first-line management of GD is ATDs for 12–18 months and RAI therapy in those with poor response to therapy or relapses. Data were obtained from outpatient records and hospital case records of all patients diagnosed as GD based on clinical and biochemical criteria (hypermetabolic symptoms, diffuse goiter, low thyroid-stimulating hormone (TSH), raised T4, T3, diffuse increased uptake on pertechnate scan) on follow-up at the endocrinology center of our hospital, a tertiary care center, Western India. Patients were included for the study based on the following criteria:

**Inclusion criteria**

- All patients of GD with hyperthyroidism diagnosed based on the standard diagnostic criteria, on ATDs for a minimum period of 12 months with additional follow-up data available for at least 6 months after RAI if administered.

**Exclusion criteria**

- Patients with GD on ATDs for whom the data regarding treatment and follow-up are available for <12 months
- Patients with hyperthyroidism due to toxic multinodular goiter or toxic adenoma.

Based on the follow-up data available, patients were categorized into following as per their duration of disease postdiagnosis: Group A – 12–18 months, Group B – 18–24 months, and Group C – >24 months. Patients were further classified based on their thyroid function status as Category 1 – hyperthyroid (on or off ATDs), Category 2 – euthyroid off ATDs, and Category 3 – hypothyroid off ATDs (at least 4 weeks after ATD discontinuation). Patients who had undergone radioablation for GD after at least a period of 12 months on ATDs for persistent hyperthyroidism were also included for analysis and the postradioablation status was recorded after a minimum of 6 months after radioablation till the follow-up data were available. As per the standard practice followed at our center, periodicity of thyroid function tests (TFTs) including TSH, T4, and T3 was monthly during ATD therapy and 3-monthly for the 1st year following attainment of euthyroid status off drugs and after radioiodine therapy and thereafter six monthly. Follow-up TFTs of those rendered hypothyroid were six monthly. Patients having persistent hyperthyroid status beyond 12 months of therapy were compared with those who had attained euthyroid or hypothyroid status. During the follow-up beyond 12 months of ATD, patients who remained hyperthyroid and received RAI therapy were further compared with those who continued to be on ATDs, for achievement of euthyroid or hypothyroid status.

Cost analysis was done for follow-ups (periodic TFTs) and treatment (ATDs and RAI) based on existing cost of these tests and drugs (for the standard dosages of carbimazole and levothyroxine) and 10 mCi of RAI which was the fixed dose administered. Fisher's exact test for categorical data and descriptive statistics for numerical data was used for analysis.

**Results**

Out of the total of 109 patients of GD on follow-up, 52 patients of GD who were on ATD for at least 12 months duration were eligible for analysis [Figure 1]. All were males. Thirty patients were on ATD for 12–18 months (Group A); 16 were on ATD for 18–24 months (Group B), and remaining six were on ATD for more than 24 months (Group C). Mean age of patients in these three groups was comparable (33.2, 35.7, and 33.3 years, respectively). The proportion of patients having goiter was similar in all the three groups. Their distribution as per thyroid function status is given in Table 1.

Statistically, the use of ATD leading to euthyroid and hypothyroid status in GD patients was only significant beyond 24 months when compared to those at <12–18 months therapy \((P = 0.0262\) and \(P = 0.0217\), respectively).

Among patients who were hyperthyroid even after 12 months or more of ATD therapy (Category 1), patients who underwent RAI therapy were assessed for response to therapy from available follow-up data after a minimum period of 6 months of radioablation. They were categorized...
as hyperthyroid, euthyroid, and hypothyroid based on the last TFT results available. The results are tabulated as in Table 2.

**Cost analysis**

Hyperthyroid patients in the three groups needed monthly follow-up until they underwent remission on ATDs or radioablation. Out of 32 hyperthyroid patients who underwent radioablation (n = 14), there were 10 patients who became hypothyroid, 3 were euthyroid, and one patient remained hyperthyroid at 6 months follow-up. Periodicity of TFTs was monthly during ATD therapy and 3-monthly for the 1st year following attainment of euthyroid status off drugs and after radioiodine therapy as per the standard guidelines. Cost analysis was done for follow-up (periodic TFTs) and treatment (drug therapy and RAI) as the case may be and compared. Cost of physician visit was not included as these services in our center are provided free of cost.

Out of eighteen patients who did not undergo radioablation, 14 remained hyperthyroid during this 6 months period and cost of follow-up of these patients was compared with the radioablation group [Tables 3 and 4].

Cost of therapy per patient beyond 12 months was lower in the RAI group compared to the ATD group (cost difference Rs. 5435.00) [Table 4].

The patients who ended up with hypothyroid status in the two treatment groups were significantly greater in RAI group compared to ATD group (P = 0.0003).

**Table 1: Characteristics and thyroid function status of Graves’ disease patients after 12 months of antithyroid drug therapy**

| Duration (months) | Total | Mean age (years) | Goiter (n) | Hyperthyroid (Category 1) | Euthyroid (Category 2) | Hypothyroid (Category 3) |
|-------------------|-------|------------------|-----------|---------------------------|------------------------|-------------------------|
| Group A (12-18)   | 30    | 33.2             | 17        | 20                        | 10                     | 0                       |
| Group B (18-24)   | 16    | 35.7             | 8         | 10                        | 5                      | 1                       |
| Group C (>24)     | 11    | 33.3             | 6         | 2                         | 7                      | 2                       |
| Total             | 57    |                  |           | 32                        | 22                     | 3                       |

**Table 2: Follow-up data of response to radioablation in hyperthyroid patients after antithyroid drug therapy for ≥12 months**

| Duration (months) | Hyperthyroid | Radioablation | Result |
|-------------------|--------------|---------------|--------|
|                   |              |               | Hypothyroid | Euthyroid | Hyperthyroid |
| Group A (12-18)   | 20           | 10            | 8        | 1        | 1           |
| Group B (18-24)   | 10           | 3             | 2        | 1        | 0           |
| Group C (>24)     | 2            | 1             | 0        | 1        | 0           |
| Total             | 32           | 14            | 10       | 3        | 1           |

**Table 3: Follow-up data of outcome of Antithyroid drug therapy for ≥12 months in hyperthyroid patients**

| Duration (months) | Hyperthyroid | ATDs | Result |
|-------------------|--------------|------|--------|
|                   |              |      | Hypothyroid | Euthyroid | Hyperthyroid |
| Group A (12-18)   | 20           | 10   | 2       | 1        | 7           |
| Group B (18-24)   | 10           | 7    | 1       | 0        | 6           |
| Group C (>24)     | 2            | 1    | 0       | 0        | 1           |
| Total             | 32           | 18   | 3       | 1        | 14          |

ATDs: Antithyroid drugs

**Table 4: Cost of investigations and treatment in hyperthyroid patients treated with radioiodine therapy compared with those on antithyroid drugs beyond 12 months duration**

| Group | Number of patients undergoing RAI therapy | Cost of RAI therapy (Rs.) | Cost of follow-up TFTs (Rs.) | Cost of ATDs/Thyroxin (Rs.) | Total Cost per patient (Rs.) | Average Cost per patient (Rs.) | Number of patients on ATDs | Cumulative cost of ATDs (Rs.) | Cost of follow-up TFTs (Rs.) | Cost of Thyroxin replacement (Rs.) | Total cost per patient (Rs.) | Average Cost per patient (Rs.) |
|-------|------------------------------------------|---------------------------|------------------------------|-----------------------------|-----------------------------|-------------------------------|----------------------------|-----------------------------|-----------------------------|---------------------------------|-----------------------------|-------------------------------|
| A     | 10                                       | 17,000                    | 17,500                       | 5355                        | 3986                        | 4219.00                       | 10                         | 34,020                      | 63,000                      | 5280                            | 10,230                      | 9634.00                        |
| B     | 3                                        | 5100                      | 4500                         | 3195                        | 4265                        |                               | 7                          | 25,110                     | 36,750                      | 3300                            | 9309                        |                                |
| C     | 1                                        | 1700                      | 1000                         | 3705                        | 6405                        |                               | 1                          | 1620                       | 3000                        | 1320                            | 5940                         |                                |

RAI: Radioactive iodine, TFTs: Thyroid function tests, ATDs: Antithyroid drugs

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**DISCUSSION**

In this retrospective, follow-up study of 57 patients of GD of more than 12 months duration, response to RAI was better than ATDs in achieving remission. Cost analysis of treatment and follow-up of these patients revealed superior economy in treating patients with radioiodine therapy in comparison with ATD beyond 12 months.

Earlier studies have shown similar benefits in terms of higher remission rates and lower relapse rates of GD with RAI therapy in comparison to ATDs. As a practice in the North America, RAI therapy is routinely offered as a first-line therapy in GD unless contraindicated. On the other hand, ATDs are routinely used as a first-line therapy in Europe and Japan. In India, RAI is used more often in those who respond poorly or relapse after ATD therapy. Greater costs, lesser availability, and apprehensions about use of radiation therapy make the use of RAI less frequent in clinical practice. Fear of inevitable hypothyroidism as an outcome of RAI therapy further makes it a second option in management of GD. There is a school of thought which promotes long-term use of low-dose ATDs in those patients who are euthyroid in this line of management with few fluctuations as a cost-effective therapy compared to RAI. Although the hypothyroidism as an inevitable outcome is avoided in this mode of therapy, the cost of frequent follow-ups, TFT monitoring, drug therapy, and likely wide fluctuations in thyroid functions with its deleterious effects on bone and cardiac health makes it a less prudent option. While studies have documented efficacy and lesser costs of therapy with RAI and surgical option for GD compared to ATDs, such studies are not available from our country. Some studies in the past have even suggested higher cost of therapy with RAI. However, lower cost of RAI in our country is the likely reason for greater cost benefit for RAI versus ATDs seen in our study.

The strengths of this study are the long follow-up and protocol-based management of all the cases in real-life practice settings. This study is limited by its retrospective design, smaller sample size, and only male patients drawn from the clientele of our medical services. ATD compliance cannot be ensured in such a setting of retrospective analysis.

Within limitations, our study highlights the benefits of early use of radioiodine therapy compared to use of ATDs beyond 12 months. With greater availability of RAI and evidence pertaining to its safety, its use as an early option in the management of GD needs consideration. Further data with stronger evidence are needed from a randomized, controlled study for comparison which is presently underway at our institution (CTRI/2016/03/006728).

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**Conflicts of interest**
There are no conflicts of interest.

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