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Outcome of Graves' Disease Patients Treated with Radioactive Iodine Therapy at RSCM: Preliminary Study

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ABSTRACT

Graves' disease (GD) constitutes 60-80% of all cases of thyrotoxicosis worldwide, typically managed with anti-thyroid drugs (ATD) as first-line therapy. If a patient failed to achieve remission after 18 months or had an ATD allergy, can continue to choose radioactive iodine (RAI^{131}) as definitive therapy. Research on the use of RAI in GD remains limited in Indonesia, and nuclear medicine facilities are not yet widely distributed. To assess the treatment outcome of fixed-dose RAI^{131} 10 mCi and the contributing factors involved. This was a retrospective observational study involving 10 GD patients who underwent RAI at RSCM. Secondary data was collected consecutively from medical records. The outcome study was the prevalence of hypothyroidism in the 3rd and/or 6th month following RAI. Serum free T4 and TSHs levels were evaluated at baseline, and at 3, 6, and 12 months post-RAI. Inclusion criteria consisted of GD patients who failed to achieve remission with ATD and subsequently underwent RAI at the Department of Nuclear Medicine, RSCM. At 3 months post-RAI, 40% of subjects achieved hypothyroidism, 40% had subclinical hyperthyroidism, and 20% reached euthyroid status. At 6 months, 80% of subjects remained with subclinical hyperthyroidism, 10% experienced worsening hyperthyroidism and 10% had developed permanent hypothyroidism. No worsening of Graves' ophthalmopathy (GO) was observed during the study period. RAI is a safe and effective definitive treatment for GD. Nevertheless, good interdisciplinary collaboration is essential to ensure the successful hypothyroidism achievement as primary therapeutic goals.

Keywords: Graves' disease, hyperthyroidism, radio-active iodine

INTRODUCTION

Graves' disease (GD) is one of the most common endocrine pathologies.[1] As an organ-specific autoimmune thyroid disorder, it's characterized by typical clinical manifestations named Merseburger trias: diffuse goiter, thyrotoxicosis and ophthalmopathy.[2,3] And the diagnoses are made based on signs, symptoms, and the result of the ancillary laboratory tests.[3]

GD prevalence is around 60- 80% of hyperthyroidism cases. Data from Cipto Mangunkusumo Hospital (RSCM), a national referral hospital, indicates that GD prevalence among all thyroid issue cases was 21% in 2004, and is projected to have grown since then. And the pathogenesis is caused by hyperfunction of the thyroid gland, which results in thyrotoxicosis and enlargement of the thyroid gland. GD often recurs, resulting in a longer duration of treatment.[3,4] Therefore early diagnosis and management of Graves' disease can prevent severe complications such as atrial flutter, atrial fibrillation, high output cardiac failure and Graves' ophthalmopathy (GO).[5,6]

Clinicians ought to be aware of systemic manifestations of Graves' disease and the different modalities available for treatment.[6] There are 3 modalities, namely anti-thyroid drugs (ATD), radioactive iodine (RAI), and thyroidectomy.[4] The choice is based on several factors such as patient age, goiter volume size, availability of modalities, response to therapy and other comorbidities.[7] In Indonesia GD is usually managed initially with ATDs, such as propylthiouracil (PTU) or Methimazole (MMI). Remission achieved in approximately half of patients after a 12–18-month duration of treatment, although it occurs in only 20-25% GD patients.[2,4,8] Patients with persistently high TSH receptor antibody (TRAb) at 12–18 months can continue ATD for the next 12 months or choose for definitive therapy with RAI or thyroidectomy. RAI has the advantage of being non-invasive and relatively safe for all ages.[8] And its main purpose is to treat hyperthyroidism by creating hypothyroidism through sufficient radiation dose to reach the thyroid tissue.[2]

Nuclear medicine has not been utilized optimally in Indonesia. Currently, nuclear medicine facilities are only available at 17 hospitals from 11 provinces of Indonesia, and more than half of them are in Jakarta. There are already around 60 nuclear medicine specialists in Indonesia and may need to be increased.[9] Furthermore there are few research on the use of RAI in GD pretreated ATD in Indonesia. This preliminary study aims to assess the outcome treatment of fixed dose RAI^{131} 10 mCi and evaluate the factors that play roles in 10 GD patients underwent RAI at Cipto Mangunkusumo General Hospital.

METHOD

This study is a retrospective observational analysis involving 10 GD subjects who failed to achieve remission with ATD and subsequently underwent RAI at RSCM as tertiary hospital. Secondary data was collected consecutively from patient medical records. Subjects previously treated with ATD were asked to stop therapy five days before RAI. All subjects were given fixed 10 mCi dose of RAI as standard treatment in our hospital and follow-up was performed at 3 months, 6 months and 12 months after. The outcome of this study was the prevalence of hypothyroid conditions in the 3rd and/or 6th month after RAI. Inclusion criteria were GD patients who underwent RAI therapy at the Department of Nuclear Medicine RSCM. Successful treatment was considered when subjects achieved hypothyroid (FT4 level range < 0,7 ng/dL or TSHs level range > 5 uIU/mL) condition in the 3rd to 6th after RAI [4]. The collected data were then displayed in the form of graphs and tabulations.

RESULT

Table 1. Characteristic data study

Variable (n=10)	Median (min-max)
Age, years	48.5 (20-59)
Uptake Thyroid Scan	34.3 (7,8-64,1)
Thyroid volume (n=8, cc)	32.3 (25,7-78,5)
TRAb (n=5)	23.6 (1,32-40)

Around 10 subjects with GD were enrolled in this preliminary study (80% female, and 20% male) as seen on table 1, all male involved having smoking habits and similar GO prevalence was seen in smoking variables. TRAb data obtained before RAI in 5 subjects with high average, and only 1 normal TRAb subject present with mild inactive GO. By 6 months RAI therapy, 20% subject start required levothyroxine (LT4) therapy, 60% decrease ATD doses, and 10% remaining increased dose. Overall, in 3 months follow-up 40% of subjects obtained hypothyroidism targets, 40% subclinical hyperthyroidism and 20% reached euthyroid status and for 6 months 80% subclinical hyperthyroidism, 10% worsening hyperthyroidism and 10% permanent hypothyroidism. No worsening of GO was observed during the study period. One subject with severe inactive GO at baseline showed no deterioration of ophthalmic symptoms throughout the 12-month evaluation.

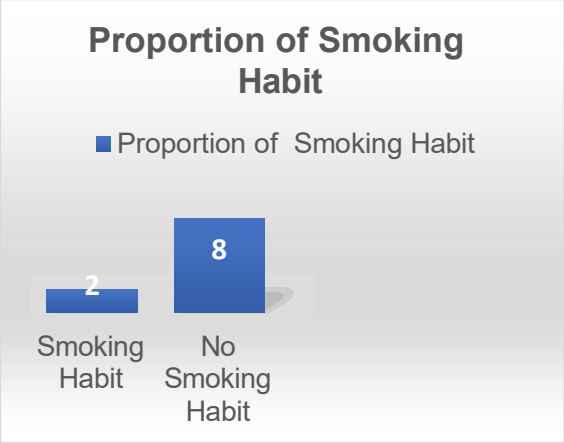

Figure 1. Proportion of smoking habit

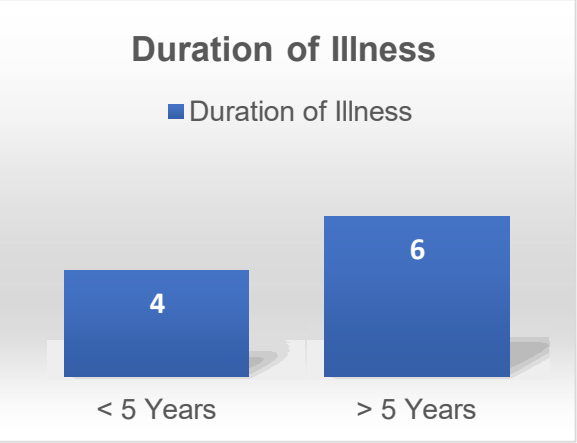

Figure 2. Duration of illness

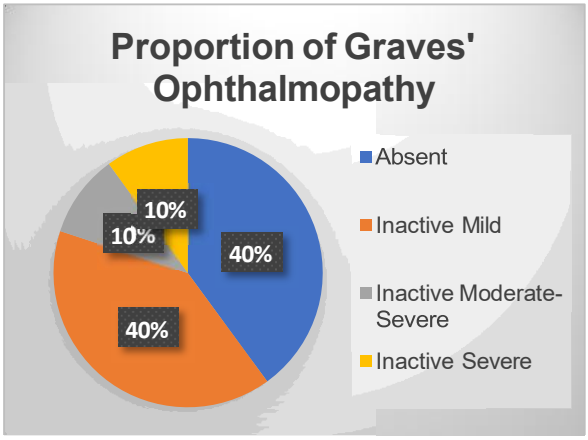

Figure 3. Proportion of Graves' ophthalmopathy

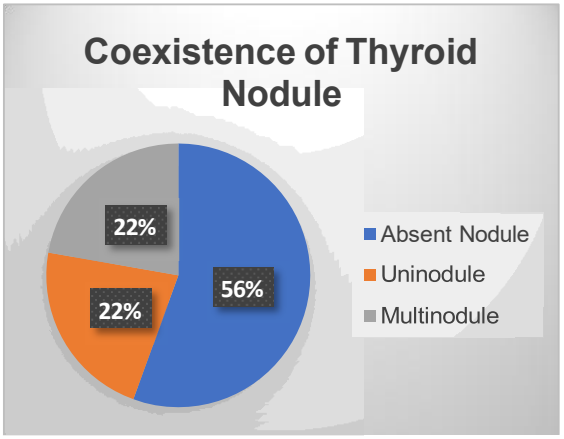

Figure 4. Coexistence of thyroid nodule

DISCUSSION

Graves' disease occupies an important position considering that it accounts for 50-80% of hyperthyroidism cases.[10,11] GD is an organ-specific autoimmune disease leading to thyrotoxicosis and goiter as main clinical feature.[2,10] The prevalence is 20–30 annual cases per 100,000 individuals with peak incidence among aged 30–60 years.[4,10] GD occurs more often in women and has a population prevalence of 1–1.5%.[8] Study at RSCM in 2004 showed GD prevalence of hyperthyroidism cases from all thyroid problems were 21%.[2] Around 8/10 samples were female with median age 48 involved in this study, in tune with GD predominance in middle-aged women.

TRAb has 99% sensitivity and specificity.[5] It is a rapid and accurate diagnostic tool for Graves' hyperthyroidism. High TRAb level is also one of prognostic for post therapy flare-up.[8] Around 4/5 samples of this study showed TRAb level > 1.75 which confirmed high disease activity status and failed to convert at 6 months follow up. The remaining subjects showed a low result that can be found in very mild GD. According to European Thyroid Association (ETA) guideline, there are no absolute indications for RAI therapy, but it is often recommended for patients with side-effects to or recurrence after a course of ATD.[5,8] Some clinical situations that favor RAI including ATD allergy, patients with periodic thyrotoxic hypokalemic paralysis, or cardiac problem.[4] It also may be considered for long standing GD (> 10 years) with small to medium goiter and inactive GO.[5] In our study almost all sample are indicated due to failed after > 18 months pretreated ATD, and only 1 subject with ATD allergy. And in line with preparation before the procedure, ATD therapy needs to be stopped 5-7 days before and may continue after in order not to decrease its efficacy.[8]

RAI efficacy has been reported in various studies ranging between 50-90% after single therapeutic dose.[2] RAI therapy success rate depend on some factors such as uptake scan, thyroid gland size, male, elderly, smoking habit, and previous ATD treatment.[5] In our study, successful outcome obtained in 40% subjects for 3 months post exposures while only 10% subject achieved permanent hypothyroidism with LT4 supplementation in 6 months. The cure rate is lower than the reported by Mohamadien et al, Yang et al, De Jong et al, and Karyampudi et al (79,7%; 76%; 74%; 61,1% respectively).[2,12,13,14]

The possible discrepancy causes are small sample size, lower fixed-dose given and delayed second dose administration. Proven by 3 among 9 failed subjects received second RAI after > 9 months follow-up obtained persistent hypothyroidism with LT4 supplementation. European Association of Nuclear Medicine (EANM) guideline stated higher fixed dose may be required when the thyroid volume >40 cc, high TRAB level, male, younger age and smoker.[5] If hyperthyroidism persists after 6 months, then a repeat RAI treatment may be needed.[6] Large thyroid volumes and high uptake are positively associated with recurrent hyperthyroidism following RAI therapy. Higher success rates can be achieved when account is taken of these poor prognostic factors.[13] Therefore good interdisciplinary collaboration is needed to maximize this goal, that all physicians engaged in therapy must be knowledgeable and incompliance with applicable law and regulations[15], patient need to be informed prior to aim and strategy of RAI, and final functional outcome including possible subsequent retreatment.[5]

There are 2 concepts for RAI therapy, functional dose concept which is correct subclinical or overt hyperthyroidism by reaching euthyroidism as soon as possible, and ablative dose concept to achieve hypothyroidism as soon as possible. But to date, EANM guideline favors the implementation of the ablative dose

concept for all GD patients due to unsatisfactory long-term outcome of GD patients treated with functional dose concept, that resulting in a higher incidence of recurrent hyperthyroidism and the risk of possible GO worsening.[5] Along with this, SNMMI guideline also denoted that decreasing the administered therapeutic activity in an effort to achieve euthyroidism can lead to prolongation of hyperthyroidism with adverse clinical sequelae.[15]

So far there is no consensus on the determination of I^{131} dose or standardization.[12,15] Meanwhile several studies also have shown comparable results of RAI in fixed-dose and calculated dose.[14] Fixed-dose regimen commonly in range 5-15 mCi, have the advantage of being simple, more convenient and lower cost. While calculated dose using 3 factors influencing therapeutic RAI activity: the RAI uptake, the thyroid size and the radiation quantity. In patients without adjunctive ATD, randomized controlled trials found 74% success with 10 mCi (370 MBq), 81% with 15 mCi (555 MBq), and 86% with 15.7 mCi (580 MBq) RAI. [4,16] In one of ETA recommendations stated no dose calculation can secure long-term euthyroidism and it's fully acceptable to offer a fixed dose of RAI.[8] Higher administration dose especially suitable for patient with nodular goiter, very large toxic diffuse goiter.[15]

Most patients respond to RAI therapy with a normalization of thyroid function tests (TFT) and improvement of clinical symptoms within 4-8 weeks. Hypothyroidism may occur from 4 weeks on, with 40% of patients being hypothyroid by 8 weeks and >80% by 16 weeks. This transition can occur rapidly but more commonly between 2 and 6 months, and the timing of thyroid hormone replacement therapy should be determined by results of TFT, clinical symptoms, and physical examination. Transient hypothyroidism following RAI therapy can manifest in 2-5 months after therapy, with subsequent complete recovery of thyroid function or recurrent hyperthyroidism.[4,5] Differentiating between transient and permanent hypothyroidism in the early months following RAI therapy remains a clinical puzzle that requires adequate clinical and laboratory follow-up to establish the optimal treatment plan, especially for GD patients with orbitopathy.[5]

RAI can have side effects including transient thyrotoxicosis, neck discomfort due to radiation-induced thyroiditis, sialadenitis, dysgeusia, permanent hypothyroidism, and new onset or worsening of Graves' ophthalmopathy. It is contraindicated in pregnant and lactating women.[10] RAI is well tolerated and complications are rare, except for those related to orbitopathy. Nwatsock et al found that RAI was associated with 3.7% of GO occurrence mainly in those who developed early (1-2 months after RAI) and prolonged (1-4 months) hypothyroid period.[16] In our study, baseline ophthalmopathy did not affect the rates of hypothyroidism after RAI. One subject was enrolled with severe inactive GO and did not show any deterioration of ophthalmopathy during 12 months evaluation. This was in concordance with Pamnani et al study, the same reason is one subject had already been pretreated with corticosteroid before.[16] Further studies, including larger prospective or retrospective cohorts, are needed to better understand the clinical outcomes of GD after RAI treatment, as well as to assess their post-treatment quality of life.

CONCLUSION

RAI is a safe and effective definitive treatment for GD. Nevertheless, good interdisciplinary collaboration is essential to ensure the successful hypothyroidism achievement as primary therapeutic goals.

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