Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

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Keywords

Graves' disease, Hyperthyroidism, Radioactive iodine, Methimazole, Carbimazole, Propylthiouracil, Graves' orbitopathy

Abbreviations

ANCA	Anti-neutrophil cytoplasmic antibody
ATD	Anti-thyroid drugs
CMZ	Carbimazole/Methimazole
EUGOGO	European group of Graves' orbitopathy
GO	Graves' orbitopathy
PTU	Propylthiouracil
RI	Radioactive iodine

Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

T3	Triiodothyronine
T4	Thyroxine
TRAb	TSH receptor antibody
TSH	Thyroid stimulating hormone
UK	United Kingdom
USA	United States of America

Abstract

Thyrotoxicosis is a common condition, most frequently due to an autoimmune aetiology (Graves' disease). There are three treatment options, anti-thyroid drugs (ATD), radioactive iodine (RI) or thyroidectomy, each with their own benefits and short-comings. Classically surgery is only used as primary treatment of Graves' disease in patients with compressive symptoms or for cosmetic reasons with the majority of patients treated primarily with either RI or ATD. In this review I will discuss and compare these two treatment modalities (RI and ATD), focussing on efficacy, safety, side-effects, cost and quality of life. Graves' orbitopathy (GO) is a rare, but potentially sight-threatening orbital manifestation of Graves' disease and the relationship between ATD, RI and GO is also discussed. ATD are the only treatment modality presently available to have beneficial effects on the autoimmune aetiology by reducing TSH receptor antibody titre. I discuss novel agents which may have utility in the future. In conclusion, RI and ATD are both appropriate primary treatment modalities. Further research is required to identify more effective treatments aimed at ameliorating the autoimmune aetiology of Graves' disease.

Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

Introduction

Thyrotoxicosis is a common condition found in approximately 0.5% of women. It is 10 times more common in women than in men and the majority of cases are attributable to Graves' disease (Tunbridge WM *et al.* 1977). Anti-thyroid drugs (ATD) (carbimazole/methimazole (CMZ) and propylthiouracil (PTU)), surgery and radioiodine (RI) are options for the primary treatment of Graves' disease. The choice of primary treatment method displays striking geographical differences, with RI therapy preferred in the USA, and ATD in Europe and Japan (Wartofsky L *et al.* 1991; Bartalena 2013). However, this is changing with a recent survey of practice in the USA reporting a fall in primary RI from 69% of endocrinologists surveyed in 1991 to 59.7% in 2011, alongside a fall amongst European endocrinologists from 25% in 1991 to 14.1% in 2013, with endocrinologists in both USA and Europe increasing their use of primary ATD (Bartalena *et al.* 2015; Burch HB *et al.* 2012). In agreement with the European survey, a recent survey of practice amongst endocrinologists in the UK found that 80% of respondents preferred ATD, 19% RI and 0.4% surgery as the initial treatment for Graves' hyperthyroidism (Vaidya B *et al.* 2008).

The ideal treatment modality should be effective, safe with minimal side-effects and cost-effective. Surgery is only rarely used as primary treatment of Graves' disease. In this review I shall compare the use of RI and ATD as treatment of this common condition.

1.0 Efficacy

In the literature a cure is defined as euthyroidism or hypothyroidism at 12 months post treatment. RI is the more effective treatment with quoted cure rates of between 70-90% for RI and 30-50% for ATD (Leary AC *et al.* 1999; Torring O *et al.* 1996a; Alexander EK and Larsen PR 2002; Cooper 2003; Peters H *et al.* 1997).

RI may be administered as a fixed dose or via individualised calculated doses, based on measured iodine uptake (uptake scan) and gland size (estimation via palpation or ultrasound). Neither approach has been demonstrated to be superior (Leslie WD *et al.* 2003; Peters H *et al.* 1995). We administer a fixed RI dose of 550MBq with resolution of hyperthyroidism at 12 months in 93% of patients with all aetiologies of primary hyperthyroidism (Lewis *et al.* 2013).

Few prospective studies have compared the efficacy of RI and ATD. One such study from a Swedish group prospectively randomised patients with Graves' disease to treatment with RI, surgery or ATD. 179 patients were followed-up for a period of 4 years. Cure rates were higher with RI (79%) than with ATD (49%). A cure rate of 94% is documented amongst those treated surgically. Of those receiving ATD 16% experienced side-effects, 6% were uncontrolled by large doses of ATD and 45% relapsed (Torring O *et al.* 1996b). A systematic review and meta-analysis reports a relapse rate of 53% with ATD and 15% with RI (Sundaresh V *et al.* 2013). A number of factors are known to increase the likelihood of relapse after ATD (thyroid volume, persistence of thyroid stimulating hormone (TSH) receptor antibody (TRAb) at completion of treatment course, smoking, post-partum period), whilst the effects of other factors (age, gender, thyroid function, presence of Graves' orbitopathy (GO)) are uncertain (Piantanida *et al.* 2015).

Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

Lithium has long been recognised to have effects on thyroid function. Its main effect is to inhibit the release of thyroxine (T4) and triiodothyronine (T3) (Lazarus 2009). The use of lithium as an adjuvant before administration of RI may improve efficacy, with an increased cure rate demonstrated in 2 retrospective studies (Martin NM *et al.* 2012; Bogazzi F *et al.* 2010). Unfortunately, this benefit has not been demonstrated in randomised studies (Bogazzi F *et al.* 1999; Bogazzi F *et al.* 2002). Further studies are required before the routine use of adjuvant lithium can be recommended.

In many centres it is standard practice to render a patient euthyroid with the use of ATD prior to administering RI. In our unit ATD are discontinued 5-7 days prior to RI and held for at least 7 days after RI administration. The use of PTU pre-treatment is associated with reduced efficacy (Bonnema SJ *et al.* 2004; Hancock LD *et al.* 1997; Santos RB *et al.* 2004). Studies examining the effects of CMZ are conflicting, with some reporting reduced efficacy (Shivaprasad and Prasanna Kumar 2015; Connell JM *et al.* 1984; Koroscil 1995), and some reporting no effect (Andrade VA *et al.* 2001; Braga M *et al.* 2002; Sabri O *et al.* 1999). A systematic review and meta-analysis reports, that ATD potentially increase rates of failure if they are given in the week before or after RI treatment, respectively (Walter MA *et al.* 2007).

2.0 Safety

Both RI and ATD have been used as treatment modalities for over 60 years and both modalities have good long-term safety records. In spite of this, concerns of increased cardiovascular disease and cancer incidence following RI administration persist.

Untreated hyperthyroidism has been reported to cause excess all-cause and circulatory mortality. This has been reported in association with patients treated with RI and this association may persist for many years after RI administration (Metso S *et al.* 2008; Metso S *et al.* 2007). It is suggested that RI through the stimulation of a localised intra-thyroidal inflammatory process may kindle a systemic inflammatory atherosclerotic process which would lead to increased risk of cardiovascular and cerebrovascular morbidity and mortality over many years (Nyirenda MJ *et al.* 2005). However it is not clear from retrospective studies whether the increased mortality is due to the underlying hyperthyroidism, the RI treatment or subsequent hypothyroidism (Franklyn JA *et al.* 1998).

It has been suggested that hypothyroidism is a desirable outcome following treatment of hyperthyroidism. Analysis of a cohort of 2668 patients who received RI showed that in those patients who were treated with replacement T4 post RI their standardised mortality ratios dropped to the same level as the background population. This study had 15,968 person-years of follow-up, and reductions were seen in both men and women (Franklyn JA *et al.* 2005).

Differentiating whether this excess cardiovascular disease is due to the hyperthyroidism or to the RI treatment is difficult and further research is required.

There are concerns of increased cancer mortality amongst patients treated with RI. Reassuring evidence that RI is a safe treatment option for young patients in the long-term is provided by a retrospective study that examined outcomes in a group of 116 patients who were treated with RI for Graves' hyperthyroidism when they were aged between 6 and 20 years of age. Patients were followed-up for a mean of 36 years. No patients developed thyroid

Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

carcinoma or leukaemia, whilst one patient developed colon cancer and one breast cancer. 62 females had a total of 179 pregnancies. This study showed no increased rate of malformations in pregnancies when compared to the rate in the general population (Read CH Jr *et al.* 2004).

A large retrospective study of 35,593 patients who were treated for hyperthyroidism in the USA, with 738,831 person-years of follow-up reports no statistically increased risk of cancer mortality amongst patients treated with RI when compared to the general US population. Whilst the numbers of patients treated with ATD alone were small, this study did report an increased mortality (standardised mortality ratio 1.31 (95%CI 1.06-1.60) from all forms of cancer in this group when compared to the US general population. This study did report an increased mortality from thyroid carcinoma amongst the patients treated with RI. The authors suggest that the majority of the patients dying from thyroid carcinoma had underlying toxic nodular goitre rather than Graves' disease (Ron E *et al.* 1998).

3.0 Side effects

Side effects occur in approximately 5% of those receiving ATD and range from minor to potentially life-threatening (Cooper 1999). Minor side effects include cutaneous rashes and gastrointestinal upset. Arthralgia may be perceived as benign but may be the portent of a severe transient migratory polyarthritis known as "the anti-thyroid arthritis syndrome" and should prompt discontinuation of the ATD (Shabtai R *et al.* 1984).

Agranulocytosis is a rare, but potentially fatal side effect. Many cases occur within the first 90 days of treatment; however it

has been documented at much later intervals also. It may also occur despite a previous uneventful course of treatment in those individuals who are receiving a subsequent treatment course following a relapse. A slightly higher incidence is documented in those receiving PTU than in those receiving CMZ (0.37% vs. 0.35%) (Tajiri J and Noguchi S 2004).

Analysis of UK adverse reaction reporting suggests that side effects are more likely to be reported for PTU than CMZ (odds ratio 2.43) and that agranulocytosis is more likely to occur and is more likely to be fatal in patients aged 65 or over(Pearce 2004).

Hepatotoxicity may occur with both CMZ and PTU, but due to different mechanisms. Hepatic abnormalities with CMZ are cholestatic in nature and recovery after discontinuation is normally the case (Arab DM *et al.* 1995). With PTU treatment, allergic hepatitis with hepatic necrosis on biopsy is seen. This can be progressive, necessitating liver transplantation and may result in death. The US Food and Drug Administration and the American Thyroid Association in a joint statement in 2009 advised that PTU is not to be prescribed as a first-line agent in children or adults. They suggest that it may be used in the first trimester of pregnancy, in life-threatening thyrotoxicosis or thyroid storm and in individuals who have experienced side effects with CMZ and for whom surgery or RI are not treatment options(Bahn RS *et al.* 2009).

Vasculitis may also occur. This may be a drug-induced lupus or may be associated with positive anti-neutrophil cytoplasmic antibody (ANCA) titres. These are more commonly seen in those receiving PTU and most commonly affects the cutaneous, renal or respiratory systems. Analysis of adverse event reporting in Japan suggests that in MPO-ANCA associated vasculitis, antibody titre is not related to severity, and

Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

may develop at any stage after commencing ATD. They report a vasculitis developing in some subjects with no detectable ANCA antibodies. They also note that only a proportion of those positive for MPO-ANCA develop vasculitis (Noh JY *et al.* 2009).

Radiation thyroiditis may occur within the first four weeks after RI administration. This is associated with neck tenderness and a small proportion of patients may become thyrotoxic. It is often treated with non-steroidal anti-inflammatories, beta-blockers or steroids. Using ATD prior to RI administration reduces the risk of this occurring (Ross 2011).

The development of hypothyroidism after RI administration is virtually inevitable, and may be a desirable outcome (Franklyn JA *et al.* 2005; Metso S *et al.* 2004).

3.1 Graves' Orbitopathy (GO)

GO is an extra-thyroidal manifestation of Graves' disease which may occur in hypothyroid or euthyroid patients, but mostly develops in a period of hyperthyroidism (Bartalena L and Tanda ML 2009). It is a rare condition that will develop in only a small proportion of patients with Graves' disease. However, GO may be sight-threatening. There are well documented concerns that RI may worsen GO. Many clinicians will avoid RI administration in patients with GO and many will prescribe a prophylactic course of glucocorticoids following RI. Identifying patients likely to develop GO, optimum glucocorticoid doses, treatments for sight-threatening GO and novel treatments with less side-effects than glucocorticoids are all areas of uncertainty requiring further research(Bartalena 2011; Bartalena 2013).

GO is rare. In a recent study of patients with Grave's disease, 73.7% had no evidence of GO, 20.2% had mild and inactive GO, 5.8% had moderate to severe and active GO and 0.3% had sight-threatening GO (Tanda ML *et al.* 2013). The clinical course is not completely understood and patients may progress, remit or remain stable over time (Perros P *et al.* 1995).

The precise aetiology of GO remains unclear, however it is likely that a reaction between T-lymphocytes in the orbit and one or more antigens shared by the orbit and the thyroid is responsible. It is likely that TRAb are involved in this process. This subsequently leads to inflammation of the extra-ocular muscles and periorbital connective tissue (El-Kaissi S *et al.* 2004).

Several non-modifiable risk factors (gender (higher incidence in women), age and genetics) and modifiable risk factors (smoking, thyroid dysfunction and elevated TRAb titre) are known. RI is classically reported as a risk factor for GO which is seen in approximately 15-20% of Graves' patients who receive RI treatment. It is possible that in those classed as developing de novo GO, what is seen is actually a worsening of already present, but not clinically apparent GO. Treatment with ATD is considered to have a neutral effect on the incidence of GO. Approximately 5% of patients who are treated with ATD will see a worsening (Traisk F *et al.* 2009; Tallstedt L *et al.* 1992; Bartalena L *et al.* 1998). However, recent analysis from 2 prospective randomised studies with 9-12 years follow-up reports no difference in incidence of GO between patients treated with ATD or RI, but did demonstrate increased incidence of GO in patients with thyroid dysfunction following their treatment, suggesting that being hyper or hypo following treatment is a significant risk factor for development of GO, a

Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

finding replicated in previous studies(Chen *et al.* 2014; Perros P *et al.* 2005; Tallstedt L *et al.* 1994).

ATD have an immune-modulatory effect with reductions in serum concentrations of TRAb, interleukins and interleukin receptors. A decrease in numbers of helper T-cells, natural killer cells, and activated intrathyroidal T-cells is also seen (Totterman TH *et al.* 1987; Wang PW *et al.* 1988). Conversely RI treatment is associated with an elevation of TRAb titre, peaking within the first year post administration and which may remain elevated for a number of years (Laurberg P *et al.* 2008). This may explain the possible increased incidence of GO in patients treated with RI.

Glucocorticoids given prophylactically have been shown to be effective at preventing progression of existing and development of GO(Bartalena L *et al.* 1998; Marcocci *et al.* 1989; Acharya SH *et al.* 2008), with a recent meta-analysis reporting a risk of progression falling from 25% to 4% in patients treated prophylactically with glucocorticoids(Shiber S *et al.* 2014). However glucocorticoids are associated with side-effects. As 80-85% of Graves' patients who receive treatment with RI do not develop GO clinicians require a system to identify those patients who stand to benefit from prophylactic glucocorticoids and exclude those patients who do not. The European Group of Graves' Orbitopathy (EUGOGO) consensus statement of 2008 recommends classifying severity as mild, moderate to severe and sight-threatening and the use of the Clinical Activity Score to assess disease activity(Bartalena L *et al.* 2008b; Bartalena L *et al.* 2008a). A number of other systems also exist including the NOSPECS and the VISA classifications (Werner 1969; Dolman PJ and Rootman J 2006). The EUGOGO consensus statement of 2008 recommends

that in the majority of patients with mild GO (active and non-active) watchful waiting is appropriate. In active moderate or severe GO prophylactic glucocorticoid cover is suggested. In inactive moderate or severe GO rehabilitative surgery is advised. In sight-threatening GO, intravenous high-dose pulsed glucocorticoids are recommended, with comment that surgical decompression may be required (Bartalena L *et al.* 2008b; Bartalena L *et al.* 2008a). However, many endocrinologists do not follow this advice and will prescribe prophylactic glucocorticoids in subjects with inactive GO also (Bartalena *et al.* 2015).

The dose or duration of glucocorticoid therapy is also not clear. A recent retrospective study showed that a low dose schedule of 0.2 mg/kg body weight for 6 weeks was effective at preventing progression in patients with initially mild or absent GO(Lai A *et al.* 2010). The EUGOGO consensus statement suggests a dose of 0.3 -0.5 mg/kg body weight commenced 1-3 days after administration of RI and tapered over 3 months (Bartalena L *et al.* 2008b; Bartalena L *et al.* 2008a). A recent meta-analysis suggests that current evidence supports a three-tier approach with the EUGOGO regimen recommended for those patients with mild to moderate GO and high risk of progression, a low dose for patients with mild GO and no glucocorticoid prophylaxis for patients without pre-existing GO and risk factors(Shiber S *et al.* 2014). The optimal dose and duration of glucocorticoids remains unclear and it is likely that a lower dose and a shorter duration than suggested by the EUGOGO consensus statement would be effective.

Unfortunately a small proportion of patients (20-30%) with severe, active GO do not respond to glucocorticoids (high dose intravenous methylprednisolone), and a further 10-20% relapse after withdrawal

Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

of glucocorticoids. In a recent multicentre trial, 4% of patients developed dysthyroid optic neuropathy in spite of intravenous methylprednisolone (Bartalena L *et al.* 2012). Orbital radiotherapy is another established treatment option for GO, usually considered as a second-line option, alongside a second course of glucocorticoids. It has beneficial effects particularly on ocular motility (Tanda ML and Bartalena L 2012). Another second-line option is a course of glucocorticoids and cyclosporine (Prummel MF *et al.* 1989). Further research is required to identify novel treatment options for this group of patients.

In patients with mild GO selenium has been shown to have beneficial effects on progression of GO. A randomised controlled trial demonstrated a six-month treatment with selenium was associated with improved quality of life, decreased eye involvement, reduced progression of GO and reduced clinical activity score at six and twelve months when compared to placebo (Marcocci C *et al.* 2011).

A number of novel agents may have utility in the future including rituximab, mycophenolate, tocilizumab, lanreotide and pasireotide (Bartalena 2013). Current research examining rituximab suggest it may be an effective option for the treatment of moderate and severe GO (Salvi M *et al.* 2013).

GO is not a contra-indication to RI treatment and in patients at high risk of development or worsening of GO an effective prophylactic treatment (glucocorticoids) exists. However, identification of those patients who are likely to benefit from prophylactic glucocorticoids, the optimal dosage and duration of glucocorticoids is also unclear. Further research to address these uncertainties is required.

4.0 Costs

There is limited data on the cost-effectiveness comparing treatment modalities. It is known that costs vary between countries. In the UK a study from the Royal Free Hampstead Hospital examined this over a 2-year period. They demonstrated a cure rate of 73% at 30 months in those treated with ATD, 95% at 24 months in those treated with RI and 100% at 24 months in those treated with surgery. The cost per cure was calculated at £3,763 per patient who received ATD, £1,375 per patient treated with RI and £6,551 per patient undergoing surgery. They speculate that over a longer period of time the cost differentials may be greater (Patel NN *et al.* 2006). A study from Sweden found the costs of RI to be 1.6 times greater than the costs of ATD over a 2-year period. However in this study patients receiving RI on average required 1.8 treatments and there was a very high rate of outpatient attendances. These 2 factors may have contributed to elevating the cost of RI (Ljunggren JG *et al.* 1998).

5.0 Quality of Life

There is limited follow-up data on quality of life following treatment of Graves' hyperthyroidism. A Swedish group have reported quality of life of the same cohort at 2(Torring O *et al.* 1996b), 3(Ljunggren JG *et al.* 1998) and 14-21(Abraham-Nordling M *et al.* 2005) years after treatment. They report no difference in quality of life scores between the three treatment modalities. Interestingly they report that even at 14-21 years after treatment these patients report lower quality of life scores than the general population. In particular vitality and mental component summary scores were lower in all groups than in the general population of Sweden. Those treated with RI reported a lower perception of general

Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

health wellbeing than those treated with surgery or ATD. The authors comment that around 50% of patients in this cohort had TSH concentrations outside the reference ranges and they speculate that this may contribute to their findings (Abraham-Nordling M *et al.* 2005).

6.0 Pregnancy

Maternal TRAb cross the placenta, stimulating the fetal thyroid and leading to fetal hyperthyroidism. In ladies previously treated with RI it is necessary to measure TRAb titre early in the pregnancy and if elevated to monitor the fetus for development of hyperthyroidism (De Groot L *et al.* 2012).

RI administration is contra-indicated during pregnancy, however successful delivery and normal childhood development following administration in the 20th week of gestation has been reported (Berg GE *et al.* 1998).

In patients with thyroid carcinoma receiving higher doses of RI for ablative purposes, no effect on fertility or male gonadal function is reported(Hyer S *et al.* 2002; Garsi JP *et al.* 2008). Some females report a transient menstrual disturbance (Vini L *et a l.* 2002)

7.0 Clinical Guidelines

The American Thyroid Association and the American Association of Clinical Endocrinologists jointly published revised guidelines in 2011, describing all three treatment modalities as effective options (Bahn Chair RS *et al.* 2011). These guidelines are widely endorsed by professional societies including the Endocrine Society and the European Thyroid Association. In a previous publication the American Association of

Clinical Endocrinologists stated that in the United States RI is currently the treatment of choice (Baskin HJ *et al.* 2002). In the UK, the Royal College of Physicians guidelines from 2007 suggest that all treatment modalities are effective options (Working Party 2007).

8.0 Future treatments of Graves' disease

It is probable that our present three treatment options have minimal effect on the underlying pathology. RI and thyroidectomy are ablative options, with RI associated with an increase in TRAb titre (Laurberg P *et al.* 2008). ATD work by blocking the uptake of iodine into the gland (CMZ), where as PTU will also block conversion of thyroxine to triiodothyronine, both within the thyroid and peripheral tissues. ATD have some immunomodulatory effects with a reduction in TRAb titre (Totterman TH *et al.* 1987; Wang PW *et al.* 1988). Treatments that work more directly on the pathogenetic mechanism are required. A Chinese group examined the effects of repeated intrathyroidal injection of dexamethasone alongside methimazole and found it reduced rates of relapse (Mao XM *et al.* 2009). This is an invasive, technically difficult procedure. It is possible that TRAb or molecules that regulate or inhibit TSH receptor signalling pathways may be developed and may have utility. Rituximab is a monoclonal antibody that targets the CD20 transmembrane antigen on the surface of pre-B and mature B lymphocytes. A number of randomised controlled trials are ongoing and it is possible this agent may have beneficial effects (Bartalena 2013; Salvi M *et al.* 2013).

Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

Conclusion

RI and ATD are both good options for the primary treatment of Graves' disease. RI is the more effective treatment option with cure rates of 70-90% after a single treatment and a recent study also suggests it is the most cost-effective option. However concerns of increased cardiovascular mortality, increased cancer incidence and of precipitating or worsening GO remain, reducing the frequency with which it is prescribed as a primary treatment. ATD are easy to take, do not require contact precautions and are frequently prescribed. They are associated with a significant rate of relapse and a number of side-effects, some of which are potentially life-threatening.

Studies comparing the long-term safety of these modalities are hampered by the significant proportion of subjects who receive ATD and relapse. These patients will often proceed to RI. Studies are often retrospective and it is difficult to ascertain if the groups are comparable.

Future research is required to examine the effects of RI on cardiovascular and cancer mortality. GO is seen more frequently in patients who receive RI, but prophylactic glucocorticoids are effective in preventing its development. Further research to identify risk factors for development of GO would allow clinicians to identify patients likely to benefit from prophylactic glucocorticoids and those who do not require them.

Ideally we would prefer to identify those subjects who will be cured after a single course of ATD. Further research in this area is required.

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Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

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Medical Research Archives
Primary treatment of Graves' disease:
Comparison of radioiodine and anti-thyroid drugs.   Vol.2 Issue 5

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Vol.2 Issue 5

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