

## CLINICAL PRACTICE

## Graves' Ophthalmopathy

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

**A 40-year-old woman who recently received a diagnosis of Graves' disease comes for a follow-up visit. She has been taking methimazole, at a dose of 10 mg daily, and is now euthyroid, but for the past 3 months, she has had bothersome eye symptoms, including redness, tearing, grittiness, photophobia, diplopia at the extremes of gaze, and ocular pain with eye movements. She smokes 10 cigarettes per day. Examination reveals exophthalmos, swelling of periorbital tissues, and limitation of eye movements. How should Graves' ophthalmopathy be managed?**

## THE CLINICAL PROBLEM

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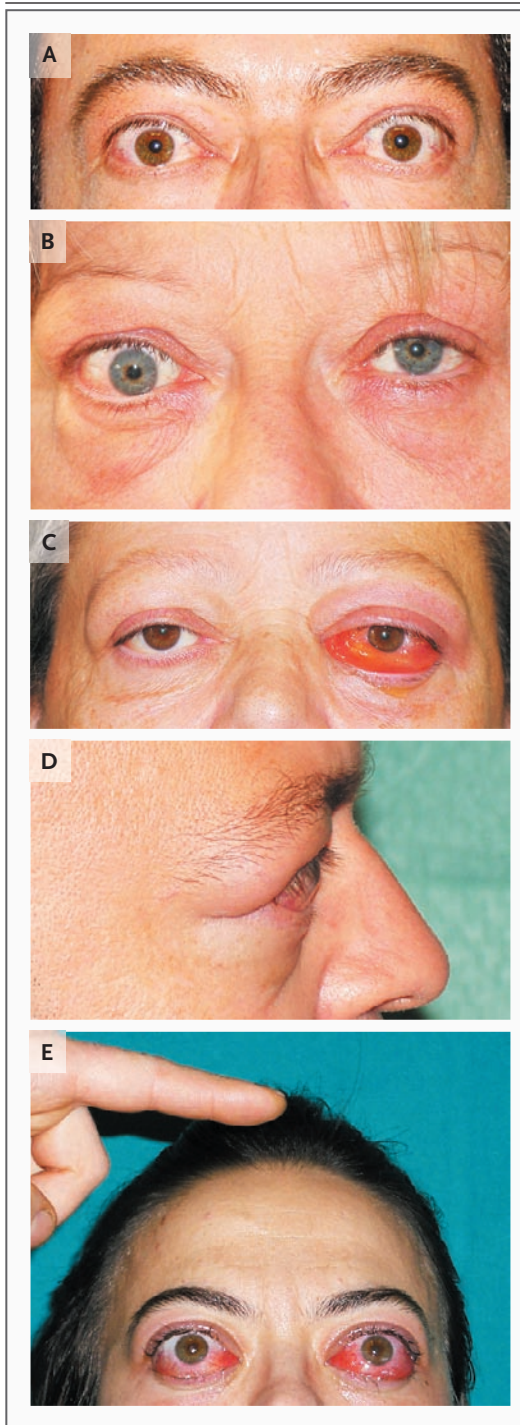
Graves' disease is often characterized by ocular manifestations of autoimmune origin, so-called Graves' orbitopathy or ophthalmopathy.<sup>1</sup> The clinical features and management of Graves' hyperthyroidism have recently been reviewed in the *Journal*<sup>2</sup>; this article focuses on Graves' ophthalmopathy.

A detailed discussion of the pathogenesis of Graves' ophthalmopathy is beyond the scope of this article, but it has been reviewed elsewhere.<sup>2,3</sup> Patients with Graves' ophthalmopathy are not necessarily hyperthyroid; a minority of patients (less than 10%) are euthyroid or hypothyroid.<sup>4</sup> Graves' ophthalmopathy is probably initiated by autoreactive T lymphocytes reacting with one or more antigens shared by the thyroid and orbit; after reaching the orbit and recognizing the shared antigen (or antigens), T lymphocytes trigger a cascade of events, including secretion of cytokines.<sup>4</sup> These cytokines stimulate the proliferation of orbital fibroblasts, expansion of adipose tissue, and secretion of hydrophilic glycosaminoglycans from fibroblasts. The resulting increase in orbital content explains many manifestations of Graves' ophthalmopathy.<sup>5</sup> B cells are also involved as antigen-presenting and autoantibody-producing cells.<sup>6</sup> The thyrotropin receptor,<sup>7</sup> the insulin-like growth factor I receptor,<sup>8</sup> or both might be the elusive shared autoantigens. Genetic determinants of Graves' ophthalmopathy remain poorly understood. Environmental factors appear to play a major role in the development and progression of Graves' ophthalmopathy.<sup>9,10</sup>

Case series from referral centers indicate that clinically recognized Graves' ophthalmopathy occurs in about 50% of cases of Graves' disease, is clinically relevant in 20 to 30%, and is sight-threatening (because of dysthyroid optic neuropathy, corneal breakdown, or both) in 3 to 5%.<sup>9</sup> Even in the absence of clinical manifestations, imaging reveals subtle orbital changes in most patients. Common bothersome symptoms, including diplopia and symptoms related to corneal exposure, such as photophobia, tearing, grittiness, and pain, may interfere with daily activities. In a cohort study, rates of eyelid retraction, exophthalmos, extraocular muscle dysfunction, ocular pain, and lacrimation were 91%, 62%, 43%, 30%, and 23%, respectively; optic-nerve dysfunction was detected in only 6% of patients.<sup>11</sup> Even mild ocu-

**Figure 1. Clinical Features of Graves' Ophthalmopathy.**

Panel A shows a man with bilateral exophthalmos and marked retraction of the upper eyelid. Panel B shows a woman with mild inflammatory signs and hypotropia in the right eye. Panel C shows a woman with marked edema and redness in the upper eyelid, redness of the conjunctiva, and severe chemosis in the left eye. Panel D shows a man with marked edema and retraction of the eyelid and exophthalmos. Panel E shows a woman with marked redness of the conjunctiva and chemosis. There is marked impairment of movement of the globes, which are unable to follow the examiner's finger; this patient had severe dysthyroid optic neuropathy, which responded dramatically to intravenous glucocorticoids.



lar changes (e.g., lid retraction, mild exophthalmos, swelling of periorbital tissues, and fixed gaze) (Fig. 1) pose cosmetic problems and may hamper social relationships.<sup>12</sup>

The natural history of Graves' ophthalmopathy is variable; ocular symptoms may progress, remain unchanged, or improve spontaneously.<sup>13</sup> Generally, there is an initial inflammatory phase (the active phase) lasting 1 to 2 years, followed by stabilization (the plateau phase), and eventually, remission (the inactive phase) occurs, but it is incomplete.<sup>9</sup>

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**STRATEGIES AND EVIDENCE**


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**DIAGNOSIS**

Graves' ophthalmopathy is usually bilateral, but it can be asymmetric or unilateral.<sup>4</sup> This condition often develops concomitantly with hyperthyroidism, but it may precede or follow hyperthyroidism.<sup>9</sup> Although the diagnosis is straightforward in patients with hyperthyroidism and bilateral ophthalmopathy, it should also be considered in patients with no thyroid dysfunction and those in whom ophthalmopathy is unilateral. Several other conditions may cause unilateral or bilateral exophthalmos or extraocular muscle enlargement. These conditions include Cushing's syndrome, obesity, orbital pseudotumor, idiopathic myositis and cellulitis, primary or metastatic orbital tumors, fistulas in the cavernous portion of the carotid artery and other vascular conditions, and granulomatous disorders. When the diagnosis is uncertain, orbital imaging with the use of computed tomography (CT) or magnetic resonance imaging (MRI) is warranted, and measurement of thyrotropin-receptor antibodies may have diagnostic value as well because of their high specificity and

sensitivity for Graves' disease. Orbital imaging in patients with Graves' ophthalmopathy shows enlargement of the extraocular muscles (with tendon sparing), an increase in orbital fibroadipose tissue, or both (Fig. 2). When dysthyroid optic neuropathy is suspected because of reduced vi-



**Figure 2. CT of the Orbits in Two Patients with Graves' Ophthalmopathy.**

In one patient, coronal sections (Panel A) show marked enlargement of the medial rectus and inferior rectus muscles bilaterally; the optic nerves (arrows) are not compressed by the enlarged muscles. In the other patient, sagittal sections (Panel B) show exophthalmos, the enlarged medial rectus, and the inferior rectus muscles; Panel C shows the results in this patient after intravenous glucocorticoid therapy. The exophthalmos is reduced, and the volume of the affected muscles is decreased.

sual acuity, visual-field defects, and reduced color sensitivity, imaging may also reveal optic-nerve compression by the enlarged muscles, particularly at the orbital apex; this is called apical crowding.

#### EVALUATION

Because the treatment for Graves' ophthalmopathy varies according to the level of its activity (i.e., active disease tends to respond to immunosuppressive therapy, whereas inactive disease does

**Table 1. Components of the Clinical Activity Score.\***

Spontaneous retrobulbar pain
Pain with eye movement
Redness of the eyelids
Redness of the conjunctiva
Swelling of the eyelids
Swelling of the caruncle
Conjunctival edema (chemosis)

\* The Clinical Activity Score is calculated according to the presence or absence of the characteristics listed. The score ranges from 0 to 7, with 0 to 2 characteristics indicating inactive Graves' ophthalmopathy and 3 to 7 characteristics indicating active Graves' ophthalmopathy. Data are from Mourits et al.<sup>16</sup>

not),<sup>14,15</sup> methods have been proposed to determine whether Graves' ophthalmopathy is active. Although no method is both specific and completely reliable, a simple office-based tool is the Clinical Activity Score,<sup>16</sup> which reflects the presence or absence of seven symptoms or signs that indicate inflammation (Table 1). One point is assigned to each symptom or sign that is present; a Clinical Activity Score of 3 or more indicates active Graves' ophthalmopathy.<sup>14,15</sup> Although imperfect, this score has been shown to be predictive of a patient's response to immunosuppressive therapy.<sup>16,17</sup>

In addition, the severity of disease should be assessed by measuring exophthalmos and lid width, evaluating soft-tissue involvement and extraocular muscle function, and assessing corneal involvement and optic-nerve involvement<sup>14,15</sup> (Table 2). Dysthyroid optic neuropathy, corneal breakdown, or both indicate that the Graves' ophthalmopathy is sight-threatening and requires immediate treatment.<sup>14,15</sup> The most frequent features of dysthyroid optic neuropathy include swelling of the optic disk, impaired color vision, radiologic evidence of apical crowding, and decreased visual acuity; marked exophthalmos and severe orbital inflammation may be absent.<sup>18</sup>

Patients with Graves' ophthalmopathy should be evaluated and treated by both an endocrinologist and an ophthalmologist with expertise in this disorder. Referral is urgent if dysthyroid optic neuropathy is suspected because of deterioration of vision, changes in the intensity or quality of color vision, or disk swelling on funduscopy, or if there is globe subluxation, corneal opacity, or lag-

ophthalmos (incomplete closure of the palpebral fissure) with visible cornea.<sup>19</sup> In all cases, selection of the appropriate treatment depends on a detailed evaluation (Table 2). A specialized evaluation is recommended early in the disease process, given evidence that the outcomes of treatment are best in cases of recent onset (within 12 to 18 months).<sup>20</sup>

#### MANAGEMENT

In all patients with ophthalmopathy, factors associated with an increased risk of progression of ocular disease should be eliminated or controlled. For instance, patients who smoke should be encouraged to quit. Although data from randomized trials are lacking, in one observational study, smoking cessation has been associated with a decreased risk of the development of exophthalmos and diplopia in patients with Graves' disease.<sup>21</sup>

Thyroid dysfunction (both hyperthyroidism and hypothyroidism) should be corrected.<sup>10</sup> In a prospective observational study, restoration of euthyroidism by antithyroid drugs was associated with an amelioration of Graves' ophthalmopathy.<sup>22</sup> In randomized trials, radioiodine therapy for Graves' hyperthyroidism caused progression of ophthalmopathy in about 15% of patients,<sup>23,24</sup> whereas antithyroid drugs did not modify the natural course of Graves' ophthalmopathy.<sup>24</sup> Risk factors for progression of Graves' ophthalmopathy after radioiodine therapy include cigarette smoking,<sup>25</sup> severe hyperthyroidism (serum triiodothyronine concentration,  $\geq 5$  nmol per liter),<sup>23</sup> high levels of thyrotropin-receptor antibodies,<sup>26</sup> and uncontrolled hypothyroidism after radioiodine therapy.<sup>27</sup> In two randomized trials, concomitant treatment of high-risk patients with oral prednisone (at an initial dose of 0.3 to 0.5 mg per kilogram of body weight given 1 to 3 days after radioiodine therapy, with tapering of the dose until withdrawal 3 months later) prevented progression and ameliorated preexisting Graves' ophthalmopathy.<sup>24,28</sup>

Prophylactic treatment with glucocorticoid agents may be appropriate for many patients with Graves' ophthalmopathy whose hyperthyroidism is treated with radioiodine therapy, including patients with active ophthalmopathy or risk factors such as those described above.<sup>14,15</sup> In a prospective observational study, patients who began to receive levothyroxine (usually 50  $\mu$ g per day initially) as early as 2 weeks after radioiodine therapy had a

**Table 2. Features of Mild and Moderate-to-Severe Graves' Ophthalmopathy.\***

Characteristic	Mild Graves' Ophthalmopathy	Moderate-to-Severe Graves' Ophthalmopathy
Eyelid retraction (mm)	<2	$\geq 2$
Exophthalmos (mm)	<3	$\geq 3$
Soft-tissue involvement	Mild	Moderate to severe
Extraocular muscle involvement (diplopia) <sup>†</sup>	None or intermittent	Inconstant or constant
Corneal involvement	Absent or mild	Moderate

\* Data are derived from Bartalena et al.<sup>14,15</sup>

<sup>†</sup> Intermittent diplopia occurs when the patient is fatigued or awakening in the morning, inconstant diplopia occurs at the extremes of gaze, and constant diplopia occurs both when the patient is looking straight ahead and when the patient is looking down.

markedly reduced risk of progression of Graves' ophthalmopathy, as compared with patients in whom levothyroxine treatment was not initiated until hypothyroidism developed.<sup>29</sup> It is unclear whether associated hyperthyroidism in patients with Graves' ophthalmopathy should be treated with antithyroid drugs or with ablative treatments (i.e., thyroidectomy, radioiodine, or both).

Specific treatments for Graves' ophthalmopathy vary depending on the severity of the disease. Mild Graves' ophthalmopathy usually does not require any treatment except for local measures (e.g., lubricants, ointments, dark lenses, and prisms to reduce diplopia) to control mild symptoms and signs.<sup>14,15</sup> In some instances, however, the patient's quality of life is so impaired that treatment such as that for more severe Graves' ophthalmopathy is warranted. Regular follow-up every 3 to 6 months is routinely warranted, since progression from mild ophthalmopathy to moderate-to-severe disease occurs in about 25% of patients.<sup>13,30</sup>

#### Glucocorticoid Therapy

Patients with sight-threatening dysthyroid optic neuropathy require immediate treatment, usually with high-dose intravenous or oral glucocorticoid agents. Although there is no established treatment schedule, a common initial regimen is the administration of 1 g of methylprednisolone intravenously for 3 consecutive days.<sup>14,15</sup> Subsequent treatment depends on the response. If there is little or no improvement after 1 to 2 weeks, patients should promptly undergo surgical orbital decompression.<sup>14,15</sup> In a small randomized trial, there was no significant difference in outcome be-

tween decompression performed as first-line treatment and initial treatment with intravenous glucocorticoids followed by oral prednisone.<sup>31</sup>

Glucocorticoids are also used for moderate-to-severe and active ophthalmopathy.<sup>9</sup> In a placebo-controlled, randomized trial, intravenous glucocorticoids (four cycles of methylprednisolone at a dose of 500 mg for 3 consecutive days at 4-week intervals) were effective in treating inflammatory changes and ocular movements in five of six patients (83%) as compared with one of nine patients (11%) who received placebo.<sup>32</sup> High-dose oral glucocorticoids (e.g., prednisolone at a dose of 40 mg or more initially) are also commonly used<sup>33</sup>; the dose is then gradually tapered until withdrawal after 4 to 6 months. An overall response rate of 63% was reported in several case series of patients treated with oral glucocorticoids.<sup>9</sup> Two randomized trials<sup>34,35</sup> have shown that intravenous therapy results in a higher rate of favorable responses than oral therapy (88% vs. 63% in one study<sup>34</sup> and 77% vs. 51% in the other<sup>35</sup>), and it is better tolerated, with a reduced risk of the development of cushingoid features.<sup>34,35</sup> However, rare cases of severe and acute liver damage (including four that were fatal) have been reported with the use of very high doses.<sup>36,37</sup> Thus, intravenous therapy should be given only with close monitoring (particularly of liver function) in specialized centers. There is no consensus regarding the optimal dose and schedule, but a commonly used regimen consists of 12 weekly infusions of methylprednisolone with a cumulative dose of 4.5 g (500 mg weekly for 6 weeks, then 250 mg weekly for 6 weeks).<sup>35</sup> These doses are much lower than those used previously; to minimize the risk of hepatotoxicity, courses exceeding 8 g are not recommended.<sup>14,15,38</sup> Oral glucocorticoids are a reasonable alternative option, particularly in patients with liver disease. Besides liver abnormalities, patients should be closely followed for other potential adverse effects of glucocorticoid treatment (e.g., increased blood pressure, hyperglycemia, electrolyte abnormalities, gastric effects, and infection).

#### *Orbital Radiotherapy*

Orbital irradiation may be a useful addition to therapy, particularly when eye motility is impaired.<sup>39</sup> In case series, about 60% of patients have had overall favorable responses to orbital irradiation,<sup>9</sup> although patients with certain features,

including exophthalmos, eyelid retraction, and soft-tissue changes, tend to have a poor response to treatment.<sup>40</sup> A common cumulative dose of radiation is 20 Gy per eye, given in 10 sessions over a 2-week period, but a lower cumulative dose (10 Gy) may be equally effective.<sup>41</sup> In a randomized trial comparing orbital irradiation with oral glucocorticoids, the efficacy rates were similar with the two approaches (approximately 50%).<sup>42</sup> Data from randomized trials indicate that combined treatment with radiotherapy and oral glucocorticoids is more effective than either treatment alone<sup>9</sup>; it is not known whether the same is true regarding intravenous glucocorticoid therapy. Orbital irradiation should be avoided in patients younger than 35 years of age (because of the potential long-term carcinogenic effects) and in patients with diabetic retinopathy or severe hypertension (because of possible additional damage to the retina).<sup>14,15</sup> To our knowledge, no cases of radiation-induced tumors have been reported in patients treated with orbital radiotherapy for Graves' ophthalmopathy.

#### *Other Possible Pharmacologic Treatments*

Randomized trials have not shown a benefit of somatostatin analogues (octreotide and lanreotide) for Graves' ophthalmopathy.<sup>43</sup> There are also few data to support the use of intravenous immune globulin for this condition.<sup>43</sup> Cyclosporine, although shown to be less effective than oral glucocorticoids in a randomized trial, may help to reduce the dose of glucocorticoids.<sup>44</sup> Preliminary data suggest that immunomodulating drugs such as rituximab<sup>45,46</sup> or inhibitors of tumor necrosis factor  $\alpha$ <sup>47</sup> may be beneficial in Graves' ophthalmopathy. In an open-label study, the effects of rituximab in patients with Graves' ophthalmopathy were similar to those observed in historical controls treated with intravenous glucocorticoids.<sup>46</sup>

#### *Surgery*

Orbital decompression is required for sight-threatening dysthyroid optic neuropathy if high-dose glucocorticoids do not ameliorate this condition within 1 to 2 weeks.<sup>14,15,31</sup> If vision is threatened by imminent corneal breakdown (which is usually associated with severe exophthalmos and lagophthalmos), and local measures and eyelid closure do not provide rapid, substantial improvement, orbital decompression is indicated to improve exposure keratopathy.<sup>14,15</sup> Orbital surgery (includ-

ing eye-muscle surgery to correct extraocular muscle dysfunction and eyelid surgery to correct eyelid retraction) may reduce the disfigurement caused by Graves' ophthalmopathy.<sup>48</sup> Surgery should be performed after ophthalmopathy has been consistently inactive for at least 6 months.<sup>14,15</sup> Orbital decompression can be performed by means of a variety of surgical techniques that are described in detail elsewhere.<sup>49</sup> If multiple surgical procedures are required for stably inactive Graves' ophthalmopathy, orbital decompression should be performed first, followed by strabismus surgery and, finally, eyelid surgery.<sup>14,15</sup> Such rehabilitative surgery can be carried out in cases of long-standing Graves' ophthalmopathy.<sup>50</sup>

#### AREAS OF UNCERTAINTY

The appropriate use of radioiodine therapy for managing hyperthyroidism in patients with Graves' ophthalmopathy remains uncertain. Some experts recommend that antithyroid drugs be used as first-line treatment in patients with active ophthalmopathy,<sup>51</sup> with the use of radioiodine therapy only later, when Graves' ophthalmopathy is inactive and if antithyroid drug treatment fails. Results of a randomized trial comparing early total thyroid ablation (thyroidectomy followed by radioiodine therapy) with near-total thyroidectomy in patients with mild-to-moderate Graves' ophthalmopathy treated with intravenous glucocorticoids suggested that total ablation results in better outcomes, although differences between groups were clinically modest.<sup>52</sup>

In patients who have received radioiodine therapy, oral glucocorticoid prophylaxis usually is recommended, but the timing of initiation and the optimal dose and duration are uncertain. The efficacy of prophylactic treatment for less than 3 months with lower doses of prednisone and longer, higher-dose treatment may be similar.

Although there is evidence to support the use of intravenous rather than oral glucocorticoid therapy for active Graves' ophthalmopathy, the optimal glucocorticoid regimen remains uncertain. It is unclear whether the addition of orbital irradiation to intravenous glucocorticoid therapy improves outcomes over glucocorticoid therapy alone. Randomized trials are lacking to compare early treatment with drugs acting on the pathogenic mechanisms of the disease (such as rituximab) with current standard therapies.

#### GUIDELINES

To our knowledge, no guidelines from professional societies on the management of Graves' ophthalmopathy are available. The European Group on Graves' Orbitopathy, a consortium of experts (endocrinologists and ophthalmologists) from eight European countries, recently published a consensus statement on the management of Graves' ophthalmopathy<sup>14,15</sup>; since there are few randomized trials, this document is based largely on expert opinion. The present recommendations are largely consistent with those in this statement.

#### CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has Graves' hyperthyroidism and moderate-to-severe and active ophthalmopathy of recent onset. A thorough eye evaluation is needed, preferably in a specialized center or by both an endocrinologist and an ophthalmologist experienced in the management of this disorder. Orbital CT and MRI provide useful information regarding extraocular muscle involvement and possible optic-nerve compression. Smoking is associated with an increased risk of progression of Graves' ophthalmopathy, and the patient should be urged to quit. Artificial tears should be prescribed.

Given the patient's active eye disease, we would recommend treatment with intravenous glucocorticoids; oral glucocorticoids are an alternative. In the absence of clinically directive evidence concerning the optimal route and dose, we use a weekly infusion of methylprednisolone (500 mg for the first 6 weeks, followed by six weekly infusions of 250 mg),<sup>35</sup> with monitoring of liver-function tests for other potential adverse effects of glucocorticoids. There are no clinically directive trials to guide treatment, but concomitant use of a proton-pump inhibitor and a bisphosphonate should be considered, particularly in patients at high risk for upper gastrointestinal complications or bone loss, respectively. Should ophthalmopathy not improve after 3 to 4 months, we recommend a second course of intravenous glucocorticoids with orbital irradiation. An alternative treatment to consider is a combination of low-dose oral prednisone and cyclosporine.<sup>43</sup> If ophthalmopathy is inactive for at least 6 months, rehabilitative surgery (e.g., orbital decompression,

strabismus surgery, or eyelid surgery) may be performed in the above order, if needed.

It is important to normalize the patient's thyroid function. Radioiodine therapy carries a risk of exacerbation of Graves' ophthalmopathy; thus, we typically prescribe oral glucocorticoid prophylaxis when we use this approach. If we treat the patient with intravenous glucocorticoid agents,

radioiodine therapy is given in the period between doses of glucocorticoids. Alternatively, antithyroid drug therapy may be continued for an 18-to-24-month course.

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