The cost of immunosuppressive therapies currently used in patients with thyroid eye disease

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ABSTRACT. Thyroid eye disease (TED) is an inflammatory condition of the orbit occurring in patients with autoimmune disease. In patients with mild TED, the most important therapeutic measure is reassurance. In severe cases, immunosuppressive therapy is the mainstay of treatment and around 10 immunosuppressive regimens have been suggested and used in such patients so far. The efficacy of these regimens varies according to the number of studies that have addressed these issues. “Response” to the treatment is also variably defined. However, to the best of our knowledge, no study has reported on the cost of immunosuppressive therapy in such patients. The aim of this study was mainly to provide information concerning the cost of different immunosuppressive regimens that patients with active thyroid ophthalmopathy undergo in different European countries. We have shown that the cheapest treatment is oral glucocorticoids (GC) and the most expensive is iv immunoglobulins. Cyclosporine is the second cheapest treatment. Radiotherapy plus oral GC have a cost between 850-3200 €; while SS analogues (SS-a) are expensive with a cost between 5000-10000 €. However, it is worth noting that the patients studied so far in this group were only few and most of them selected on a basis of a positive octreoscan, the cost of which has to be considered when choosing this type of treatment. Germany is by far the most expensive country as regards the costs of the main remedies, whereas Greece is the cheapest. Denmark is the most expensive country concerning radiotherapy, while Germany is the cheapest. (J. Endocrinol. Invest. 27: 919-923, 2004) @ 2004, Editrice Kurtis

INTRODUCTION

Thyroid eye disease (TED) or Graves’ orbital disease or thyroid ophthalmopathy is an inflammatory condition of the orbit occurring in patients with autoimmune thyroid disease (1, 2). It affects about 50% of patients with clinically evident Graves’ disease (3). Severe TED occurs in about 3-5% of all cases. In patients with mild TED, the most important therapeutic measure is reassurance, whereas immunosuppressive therapy is the mainstay of treatment in severe cases taking into account the autoimmune nature of the disease (4). Available immunosuppressive regimens and their commonly used doses are shown in Table 1. The efficacy of these regimens varies in different studies due to biases in the selection of patients, especially concerning the different degrees of disease activity and duration of eye disease. “Response” to the treatment is also variably defined. However, to the best of our knowledge, no study has reported on the cost of immunosuppressive therapy in such patients. The aim of this study was mainly to provide information concerning the cost of different immunosuppressive regimens that patients with active thyroid ophthalmopathy undergo in different European countries.

CURRENT USED IMMUNOSUPPRESSIVE THERAPIES

Glucocorticoids (GC)

It has been shown that GC can inhibit the synthesis and release of glycosaminoglycans (GAGs) by orbital fibroblast in vitro, a key mechanism in the pathogenesis of the disease (2, 5). The efficacy of oral prednisone is approximately 65% (6). Various uncontrolled studies have suggested that GC administered by iv route are more effective than oral

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Key-words: Thyroid eye disease, cost, immunosuppressive therapy, somatostatin analogues.

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prednisone with fewer side effects (6). A cure is seldom achieved with GC therapy and a great number of patients require additional forms of therapy, usually major orbital surgery (7, 8).

**Orbital radiotherapy (ORT)**
The efficacy of this treatment is approximately 55% (6). The combination of ORT and GC is more effective than either one alone, as was shown in two randomized clinical trials performed by the Pisa group (9, 10).

**Cyclosporine (CLS)**
CLS is especially effective in inhibiting a new immune response, but is ineffective in ophthalmopathy as monotherapy. It seems to be beneficial when combined with GC (11, 12). In 1989, Prummel et al. (8) found that the response rate to steroids was 61% at 3 months after initiation of therapy, whereas only 22% in patients treated with CLS alone. Moreover, the combination of a lower dose of prednisone with CLS improved the eye signs of 59% of the patients who had previously not responded sufficiently to GC alone. In 1986, Kahaly et al. (13) performed a randomized clinical trial comparing the combination of CLS and GC with GC alone and found that CLS with GC was slightly more effective.

**SS analogues (SS-a)**
Octreotide was first given to patients with TED by Chang et al. (14). In a controlled study, comparing octreoscan-positive with octreoscan-negative patients, SS-a were mainly useful in patients with positive octreoscan (15). This experience has been extended by reporting additional patients selected by octreoscan positivity (16). The response rate of SS-a treatment in patients with TED is approximately 70% (16).

**Iv immunoglobulins (IVIG)**
Most IVIG preparations contain the powerful immunosuppressive cytokine TGF-beta, which may explain the therapeutic effects (17). The response rate is approximately 60-65% (18, 19). In 1996, Kahaly et al. (18) found that IVIG and oral GC had similar response rates: 62 vs 63%. These data were confirmed one yr later by another study by Baschieri et al. (19). This treatment is laborious as the patient needs to travel to the clinic.

**METHODS**
Information concerning the costs of immunosuppressive regimens currently used in 9 European countries, with the only exception of The Netherlands, were collected by approaching individual colleagues specialists in the field. However, some of the responders could not provide information for all the regimens currently used, either because the specific remedy was not available in their countries or for other non-specific reasons. As regards the Netherlands, the data were reproduced from reference 20. The 9 countries involved are: Germany, Italy, UK, Spain, The Netherlands, Greece, Belgium, Denmark and Sweden. The names of the colleagues who provided the information are listed in the acknowledgement section of this manuscript. Only the prices of individual remedies are included in the cost estimate. Table 2 provides data for extra treatment costs, where applicable. The efficacy of each regimen was assessed on the basis of therapeutic outcome, which was supported by an extensive Medline literature search. However, one must bear in mind that, even though an overall response rate to steroids and radiotherapy can be given with some confidence, due to the large number of studies performed and also to similarities to the patients studied, this is not the case with the other therapeutic regimens. Few studies have been published so far with limited number of patients.

**COSTS OF DIFFERENT REGIMENS**
The costs of currently used immunosuppressive regimens in different countries in Europe are presented in Table 2. As shown in this table, the cheapest treatment is oral GC followed by IV steroids. However, in most centers IV GC pulse therapy is given only to hospitalized patients and the cost of hospitalization should be added in the whole cost of this type of regimen. The most expensive treatment is IVIG. Cyclosporine is the second cheapest treatment. The average cost for ra-

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial dose</th>
<th>Duration of treatment</th>
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</thead>
<tbody>
<tr>
<td>Oral prednisone</td>
<td>60-100 mg/day</td>
<td>4-6 months</td>
</tr>
<tr>
<td>Pulses of 0.5-1 g for 3 days, often repeated for 1-7 weeks</td>
<td>followed be 20 mg of oral prednisone for total of 4-6 months</td>
<td></td>
</tr>
<tr>
<td>Iv methylprednisolone</td>
<td>100 mg tds</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Octreotide</td>
<td>40 mg every 2 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Lannreotide</td>
<td>10x2 Gy</td>
<td>2 weeks</td>
</tr>
<tr>
<td>ORT</td>
<td>5-7.5mg/kg +20 g for oral prednisone</td>
<td>12 weeks</td>
</tr>
<tr>
<td>CLS</td>
<td>1g/kg for 2 days</td>
<td>repeated 5-6 times every 3 weeks for 4-5 months</td>
</tr>
</tbody>
</table>

Adapted from ref. 20. CLS: cyclosporine; IVIG: iv immunoglobulins; ORT: orbital radiotherapy.