OCTREOTIDE SCINTIGRAPHY IN THYROID ORBITOPATHY

GAMMA GRAPÍA CON OCTREÓTIDO EN LA ORBITOPATÍA DISTIROIDEA

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ABSTRACT

Introduction: Graves’ disease, which has an autoimmune basis, is associated with the infiltration of activated lymphocytes into the retrobulbar tissues of the eye. These activated lymphocytes express somatostatin receptors on their surface which mediate the inflammatory response.

Objective: To evaluate the efficiency of $^{111}$In-Octreotide scintigraphy in the identification of orbital activity in Graves’ disease and the usefulness of treatment with a somatostatin analogue, based on a pre-established protocol within the Nuclear Medicine Department.

Methods: We studied a group of eighteen patients with symptomatic Graves’ ophthalmopathy of between two months and four years duration. We injected 6 mCi of $^{111}$In-Octreotide parenterally, and performed scintigraphy four and twenty-four hours later. Four patients, all in the active phase, showed orbital somatostatin receptors, for which they were treated with lanreotide 60 mg every fifteen days for three months. Patients were reviewed after 3

RESUMEN

Introducción: La enfermedad de Graves es una enfermedad de base autoinmune en la cual existe una infiltración por linfocitos activados en el tejido retroorbitario. Estos linfocitos activados se caracterizan por aumentar la expresión de receptores de somatostatina en su superficie que median la respuesta inflamatoria.

Objetivo: Valorar la efectividad de la gammagrafía con $^{111}$In-octreótido en la identificación de actividad orbitaria en la Enfermedad de Graves y valorar qué pacientes son subsidiarios de recibir tratamiento con análogos de la somatostatina, así como su evolución con el tratamiento, según un protocolo establecido con el Servicio de Medicina Nuclear.

Métodos: Se estudió un grupo de dieciocho pacientes con oftalmopatía tiroidea sintomática de dos meses a cuatro años de evolución. Se les inyectó 6 mCi de $^{111}$In-octreótido vía endovenosa siendo estudiados mediante SPECT a las cuatro y veinticuatro horas. Cuatro enfermos, todos en fase activa, mostraron captación orbitaria, por lo que fueron tra-
INTRODUCTION

Thyroid orbitopathy (TO) is a disease of a highly variable clinical and aesthetical severity which fundamentally affects middle-aged women. The literature describes a high number of thyroid diseases that can produce alterations in ocular structures, but the Basedow Graves disease is the thyroid disease with which it is related more often (90%); although only 10-12% of these patients suffer it (1).

The TO consists of two phases: the phase of active inflammation lasting between 6 and 18 months, and the inactive phase in which the inflammation disappears (the phase does not become active). The active phase exhibits inflammatory damage giving rise to different symptoms like conjunctival chemosis, keratoconjunctivitis, palpebral retraction, temporary anomalous ocular movements and dyplopia, proptosis, ocular hyperpressure and optical neuropathy. This inflammation can, in some cases, culminate in irreversible muscular fibrosis (2).

The fundamental mechanisms of the development of the orbitopathy are not yet known. However, it is possible that such antithyroid autoantibodies attack certain cellular types present in the orbit. However, the presence in the active phase of a lymphocyte infiltration in the ocular soft tissues is proven, accompanied by a mitotic and maturing stimulation of adipocytes and fibroblasts (3). The extraocular muscles increase their volume at the expense of their connective component (1), which can later on produce motor alterations and restrictions.

For some years, we have known the expression of somatostatine receptors by the lymphocytes present in that affected retrobulbar tissue, but only during the active phase of the disease (4). The presence or absence of these receptors can be studied by means of objective tests which utilize the radiation emitted by somatostatine analogous drugs such as the octreotide, together with radioactive molecules (3). This would help us to differentiate the active TOs, since clinically it is often difficult (4), and therefore to more suitably indicate the treatments which are different from those utilized in the fibrosis phase (3,5,6).

Traditionally the handling of the active phase is based on the minimization of the inflammation and edema by means of immunosuppressants, with clear predominance of anti-inflammatory steroids, with x-rays and surgery in reserve. The latter is utilized in this period only for serious complications which force an urgent retro-orbitary decompression (1). The greater the severity of the TO, the better will be the answer to the immunosuppressant treatment (7).

Recently the somatostatine analogs are an option to handle these patients, being based on their inhibition of the proliferation and activation of the lymphocytes (6,7). According to some authors, said analogs could even become an alternative to glucocorticoids (4).

In the phase of sequel only surgery can improve the patient’s quality of life. The most important expressions are established dyplopia which in many
occasions require ocular surgical treatment on the extrinsic muscles, as well as the palpebral retractions which can be corrected with «müllerectomies», muscular weakening, or with «palpebral spacers», according to each case.

The suitable handling of symptoms related to eye lubrication problems must always be taken into consideration. Usually, artificial tears provide moderate relief and will satisfy most patients (1).

Our objective in this work is to value the effectiveness of the SPECT (acronym of «Single Photon Emission Computed Tomography») with In\(^{111}\) ocreotide to identify orbital activity in patients with Graves disease and to assess the candidates to be treated with immunosuppressants, as well as the evolutionary response to three months of treatment with somatostatine analogs.

**SUBJECTS, MATERIAL AND METHOD**

Eighteen patients affected by TO, fourteen of them women, were subjected to gammagraph with somatostatine receptors to assess the presence or absence of orbital activity. All the patients had been diagnosed previously of Graves disease in a period of time between 2 and 45 months (mean: 27 months). The age average was of 34.5 years. Some were presumed to be in inactive stage due to their evolution time, but if they exhibited any ocular symptom, after being informed and accepting, they were subjected to gammagraphy in order to assess in this way some degree of activity and specificity.

A 6 mCi injection of intravenous In\(^{111}\)octreotide was administered each patient, making planar images and tomographic study by means of SPECT at four and twenty-four hours (fig. 1). These images were assessed by valued by Nuclear Medicine specialists who decided the presence or absence of activity at orbital level using a qualitative contrast method, comparing the orbital absorption vis-à-vis the fundus absorption (occipital bone tissue) (fig. 2).

Four patients exhibited absorption of the radiotracer, bilaterally although asymmetrically, all in clinically active phases.

The fourteen patients who were considered negative were reassessed clinically after 2 to 5 months, without any immunosuppressant treatment because we considered that gammagraphically they were
already in the second phase and would not respond to any treatment. Of said 14 patients, three had been assessed as clinically active (two slight degree with 22 and 25 months of evolution, and one moderate with 13 months of evolution). The remaining eleven exhibited a score of clinical activity (PAC) below 2 and had been assessed as inactive, with an evolution time between 20 and 45 months.

Patient 1 was a 44 year-old man, a smoker, who went to the Urgency Service due to an important bilateral keratoconjunctivitis which did not respond to the usual treatments, with negative microbiological study. In a consultation with Endocrinology he was diagnosed with a thyroid alteration. He exhibited ocular hypertone: right eye (RE): 32 mmHg, and 28 in the left eye (LE); exophthalmos of 25 mm in RE and 24 in the LE; and palpebral retraction of 3 mm in both superior eyelids with 2 mm in inferior eyelid of RE and 1 in the LE. The external ocular movements (EOM) and the rest of exploration were within normal ranges. According to the NOSPECS severity classification, a moderate degree was considered. The patient was treated 2 months after the beginning of the symptoms.

Patient 2 was a 54 year-old woman who visited the Ophthalmology practice due to pain in the LE and dyplopia transitory. In the biomicroscopic study she evidenced a slight bilateral keratoconjunctivitis and intraocular pressure values of 20 mmHg in each eye. She did not exhibit exophthalmos nor palpebral retraction. Upon exploration of EOM she exhibited a deficit in LE supraduction. As with patient 1, a consultation with the Endocrinology Service diagnosed thyroid alteration in active phase and moderate degree, beginning treatment 15 months after the beginning of the symptoms.

Patient 3 was a 30 year-old woman diagnosed with Graves diseases 6 months earlier, referred from the Endocrinology Service by ocular alterations. She exhibited a slight bilateral keratoconjunctivitis with 18 mmHg of intraocular pressure in both eyes, exophthalmos (25 mm in RE and 23 in the LE), and bilateral palpebral retraction: RE with 2 mm of elevation from the upper eyelid and 1 from the lower one, and in the LE 1 mm in both eyelids. EOM and the rest of the exploration were normal. The severity was slight moderate and was treated 4 months from the beginning of the ocular symptoms, in active phase.

Patient 4 was a 27 year-old woman who, like the anterior one, was referred by the Endocrinology Service assessment and treatment of ocular symptoms. She had been diagnosed with Graves disease 16 months earlier. She exhibited a slight bilateral keratoconjunctivitis with ocular pressure of 20 mmHg in the right eye and 19 in the left one, with exophthalmos of 27 and 24 mm respectively. Palpebral retraction of 3 mm in RE upper eyelid, and 2.5 mm in both lower eyelids. EOM and rest of exploration was normal. She was considered to be in active phase, moderate degree, beginning the treatment 10 months after the symptoms started.

These four patients were diagnosed with Graves disease and TO, requiring control of the thyroid function by the Endocrinology Service, and their orbitopathy was treated with lanreotide 60 mg (Somatulina Autogel®; Pisen Pharma, S.A.; Barcelona, Spain), analog of somatostatine having a long average life, in intramuscular injection (alternating gluteus) every fifteen days for three months. Aster this time, they were subjected once more to an orbital SPECT to study changes in the orbital activity, and in addition they were clinically reassessed to verify agreement between clinical symptoms and gammagraphy.

RESULTS

All the orbits that had been classified as positive in the first SPECT captured with significantly less intensity in the second, after the treatment with somatostatine analogs. In addition the symptoms reduced considerably in patients 1, 3 and 4.

None of the fourteen patients who turned out to be negative showed significant clinical changes with in the assessment respect to their anterior state.

Patient 1 (moderate degree) no longer referred ocular surface symptoms in a few weeks after beginning the treatment, and she only needed lubrication thereafter. We verified a reduction in the exophthalmos of two millimeters in each eye (up to 23 and 22 mm RE and LE respectively) and of the palpebral retraction down to only one millimeter in both upper eyelids. There was a clear gammagraphic improvement (fig. 3).

Nevertheless, the intraocular pressure could not be controlled with topical medical treatment, exhibiting 30 mmHg in RE and 36 in the LE. This patient finally required surgical solution in the LE, whereas the right reached 16 mmHg with maximum medical treatment after three weeks of the post-tre-
Treatment evaluation, concomitant with the intervention of the other eye, which involved almost four months in treatment with Somatulina Autogel®.

Patient 2 (moderate severity) did not improve clinically although the gammagraphic results showed improvements. She only referred improvement of pain but the remaining symptoms, dyplopia, had worsened. This was confirmed by the Test of Lancaster, which also showed alterations in the inferior rectum of the RE (fig 4).

In addition the intraocular pressure had to be controlled with analogs of topical prostaglandins. As it continued exhibiting receptors somatostatine according to the second SPECT, a new lanreotide dose was administered. After the fourth dose, the clinical symptoms improved and the intraocular pressure returned to normal values. After this second cycle we continued with corticoid treatment that was suspended after four months because it did not contribute any improvement.

Patient 3 (moderate degree) exhibited improved exophthalmos, with a 2 mm reduction in RE and 1 in the LE, and of the palpebral retraction, showing 2 mm of sclera in the upper RE and 1 mm inferiorly in this same eye. In the LE no palpebral retractions were appraised. The rest of exploration did not reveal changes.

Patient 4 (moderate degree) exhibited improved keratoconjunctivitis, only needing maintenance with artificial tears. The exophthalmos was reduced 1 mm in both eyes. The pressure remained at 18 mmHg in the RE and 19 in the LE. The superior palpebral retraction of the RE diminished 2 mm. As the other patients, the SPECT showed improvement (fig. 5).

**DISCUSSION**

Of the eighteen studied patients, seven were estimated to be in active phase according to their clinical activity, four of them in moderate degree, one slight moderate, and two slight ones, considering the other eleven to be inactive. The four positive patients in the SPECT were already considered active according to clinical symptoms, three of moderate severity and one slight moderate. The other three active but clinically negative patients according to SPECT, two slight and a moderate one (22, 25 and 13 months of evolution), did not show changes in the three-month assessment, in all cases they improved without immunosuppressant treatment.

It must be emphasized that all patients with more than 15 months of evolution showed negative in the SPECT, with patients having lower evolutions (2, 4, and 10 months) showing positive results. For that reason, after that time it seems that SPECT is not very useful.

Considering the above, we thought that the SPECT with somatostatine analogs with radioactive markers has been useful to indicate medical treatment to patient affected by TO due to Graves disease because it helps to differentiate the active phase from non-active phases of this pathology (2,5,6).

The patients treated with lanreotide demonstrated a smaller orbitary capture and therefore a smaller ocular inflammatory activity after three months of treatment with immunosuppressants. However, in one of the four patients this smaller capture was not related to a significant clinical improvement.

*Fig. 3: SPECTs of patient 1. Above: before treatment. Below: after treatment.*
In our series of cases, after the treatment the exophthalmos and the palpebral retraction improved partially in all the patients who exhibited these symptoms. However, the miopathy was not altered at the clinical level and the intraocular pressure did not show significant changes either. The visual acuity did not exhibit changes in any patient. The expressions related to the ocular surface are the only thing that improved more and faster, with maintenance treatment with artificial tears being necessary.

It is worth noting the near absence of side effects (diarrhea in patient 2).

Given the characteristics of the study, we cannot compare the effectiveness of lanreotide with glucocorticoids. We can only comment that patient 2 did not improve with any treatment because she was either in the inactive phase (most likely considering the time of evolution), or simply did not respond.

However, clinical tests have not demonstrated the effectiveness of somatostatine analogs or their advantages over glucocorticoids or correlation between SPECT and the effectiveness of the treatment (9,10). However, there is agreement in that clinical activity predicts the response to immunosuppressants (8).

The SPECT with ocreotide is a hardly invasive and simple image test which, in our experience and that of other authors (2,3), is useful to detect the active phases of TO which can be treated with immunosuppressants, as well as to predict the response somatostatine analogs in patients with Graves disease. It could also be an indicator of response to corticosteroids (5).

The results of the treatment seem to largely depend on the selection of patients (under eleven months in our series of cases). It is important to have patients in the first stage of active inflammation, and an objective way to consider it can be the SPECT.

Fig. 4: Patient 2. Left: SPECT and Lancaster pre-treatment. Right: SPECT and Lancaster after treatment. We observed that there is no clinical-gammagraphic match, observing lower capture but more dysplopia.
New revisions and a more extensive series of cases will allow to collect more data which will help us to confirm or dismiss these initial results.