Original article

Treatment by rituximab on six Grave’s ophthalmopathies resistant to corticosteroids

Traitement par rituximab de six orbitopathies dysthyroïdiennes résistantes aux corticoïdes

Flavien Précausta a,*, d, Sophie Arsène a, Peggy Renoult-Pierre b, Boris Laure c, d, Lise Crinière b, Pierre-Jean Pisella a, d

a Service d’ophtalmologie, hôpital Bretonneux, centre hospitalier universitaire de Tours, 2, boulevard Tonnellé, 37044 Tours cedex 9, France
b Service de médecine interne, hôpital Bretonneux, centre hospitalier universitaire de Tours, 2, boulevard Tonnellé, 37044 Tours cedex 9, France
c Service de chirurgie maxillofaciale, avenue de la République, centre hospitalier universitaire de Tours, hôpital Trousseau, 37170 Chambry-lès-Tours, France
d Faculté de médecine de Tours, 10, boulevard Tonnellé, BP 3223, 37032 Tours cedex 1, France

Abstract

Objectives. – Grave’s ophthalmopathy occurs in 50% of Graves’ disease cases. Treatment is based on smoking cessation, and control of the euthyroidism and ocular repercussions associated with the disease. The active orbital forms are treated with glucocorticoids. Non-validated therapies have also been recently tested. Rituximab has been effectively used several times to treat corticosteroid-resistant Graves’ ophthalmopathy associated with an optic neuropathy, but its use could be proposed only in inflammatory ophthalmopathies after failure of the corticosteroids. We present six cases treated since early 2012 at the University Hospital Center of Tours, France. Methods. – Six patients were treated at the University Hospital Center of Tours, France, between September 2012 and April 2014. The patients had a Mouriès’ score greater than three after treatment with corticosteroids and/or a severe NOSPECS score and/or orbital inflammation resistant to maximal treatment with intravenous injections of methylprednisolone and an optic neuropathy. They twice received one gram of rituximab by slow intravenous injection two weeks apart. Efficacy was assessed by a decrease of the orbital inflammatory clinical Mouriès’ score, and visual acuity and visual field testing. Results. – The inflammatory score of patients improved and treatment helped to stop the progression of the sequelae due to neuropathy. The orbital inflammatory clinical score, and the visual acuity and visual field improved but orbital decompression was necessary to complete the treatment. Conclusion. – Rituximab has been used for the treatment of active corticosteroid-resistant Graves’ ophthalmopathies. We also had positive results on patients with visual threat and optic neuropathy, when combined with surgical decompression.

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Keywords: Graves ophthalmopathy; Rituximab; Anti-CD20; Optic neuropathy

Résumé

Introduction. – L’orbitopathie basedowienne survient dans 50% des maladies de Basedow. Son traitement repose sur l’arrêt du tabac, l’euthyroïdie et le traitement du retentissement oculaire (symptômes et séquelles). Le traitement de l’orbitopathie active aiguë repose sur la corticothérapie, cependant plusieurs autres thérapeutiques non validées sont à l’étude. Le rituximab a été utilisé à plusieurs reprises efficacement pour traiter des atteintes orbitaires graves avec atteinte du nerf optique, quand celles-ci étaient résistantes aux corticoïdes, mais son utilisation ne pourrait être proposée que dans l’indication inflammatoire après échec des corticoïdes. Nous présentons ici six cas traités au centre hospitalier universitaire de Tours depuis début 2012. Matériels et méthodes. – Six patients ont été traités au centre hospitalier universitaire de Tours entre septembre 2012 et avril 2014, présentant un score de Mouriès supérieur à trois, persistant après la corticothérapie, et/ou un score NOSPECS sévère, et/ou avec une inflammation orbitaire résistante à un traitement maximal par bolus de Solumédrol®, et une neuropathie optique. Ils ont reçu un gramme de rituximab en perfusion lente intraveineuse, à deux reprises à deux semaines d’intervalle. L’efficacité a été évaluée sur la diminution du score inflammatoire clinique orbitaire de Mouriès, l’acuité visuelle et le champ visuel. Résultats. – Les patients traités ont amélioré leur score inflammatoire et le traitement a permis d’éviter l’aggravation des séquelles de la maladie dans les formes avec neuropathie. Le score inflammatoire orbitaire a été amélioré ainsi que l’acuité visuelle et le champ visuel. Un traitement par décompression orbitaire a été nécessaire en complément dans tous les cas.

* Corresponding author.
E-mail address: Flavien.precausta@univ-tours.fr (F. Précausta).

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Conclusion. – Le rituximab a été utilisé dans les orbitopathies dysthyroïdiennes actives résistantes aux corticoides. Nous avons eu également des résultats positifs pour nos patients avec menace visuelle et neuropathie optique résistantes aux corticoides, en complément de la décompression chirurgicale.

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Mots clés : Orbitopathie basedowienne ; Rituximab ; Anti-CD20 ; Neuropathie optique

1. Objectives

Graves’ ophthalmopathy is a disfiguring and potentially blinding disease, which greatly affects the appearance of patients and their quality of life. It affects the eyelid and the area around the orbit combining proptosis, oculomotor disorders, and eyelid abnormalities. The incidence of Graves’ disease is 16 per 100,000 for women and three per 100,000 for men per year [1]. Graves’ ophthalmopathy occurs in 50% of these patients and can be severe in 3–5% of cases. The symptoms can range from a sensation of dry eye, photophobia, excessive watering, and binocular diplopia, to damage to the optic nerve resulting in visual loss and/or visual field defects.

Several factors have been found to be associated with the severity of symptoms including being male, thyroid hormonal imbalances [2], and tobacco use, which is the most important modifiable risk factor. Immunosuppressive therapies are also less effective in smokers. The most common clinical manifestations are upper eyelid retraction, edema, erythema of the periorbital tissue and conjunctiva, and proptosis. Symptoms are related to the increase of soft tissue in the orbital cavity associated with mononuclear cell infiltration into the extraocular muscles, lacrimal glands and fat tissue. Disease activity is quantified by the Mourits’ clinical inflammatory score [3] amended by the European Study Group on Graves’ orbitopathy EUGOGO [4].

The diagnosis of Graves’ ophthalmopathy is based on clinical characteristics, but imaging can aide diagnosis; CT evaluates the severity of proptosis, magnetic resonance imaging visualizes the inflamed tissues, and ultrasound quantifies the level of edema and inflammatory cell infiltration.

The infiltrating mononuclear cells are mainly CD4+ T lymphocytes, which are activated by antigen presenting cells such as B cells. These T cells cause a local inflammatory reaction by activating fibroblasts and secreting cytokines such as IL-2, IFN-γ, and TNF. The fibroblasts synthesize hyaluronic acid and some of them differentiate into mature adipocytes. These changes result in a volume increase of muscles and orbital fat. The origin of the orbital location of inflammation is poorly understood; fibroblast proteins acting as autoantigens has been suggested [5].

The standard treatment for Graves’ ophthalmopathy is IV glucocorticoid therapy [6]. Rituximab, directed against the CD20+ lymphocyte marker is already used to treat various pathologies, such as non-Hodgkin lymphoma and rheumatoid arthritis. It has been repeatedly used to treat Graves’ ophthalmopathies when they were resistant to corticosteroids because of its action against B cells, which strongly contribute to orbital inflammation. It has been effectively used in some cases with optic neuropathy [7–14]. However, its use could be proposed only in inflammatory ophthalmopathies, if corticosteroids have failed, and non-recommended in optic neuropathy according to the last guidelines in 2016 because of the development of optic neuropathy after a rituximab treatment in some cases [6].

We present six cases treated at the University Hospital Center of Tours, France, since early 2012.

2. Methods

Six patients were treated with rituximab between September, 2012 and April, 2014 for Graves’ ophthalmopathies at the Tours University Hospital Center, France. They had a Mourits’ inflammatory clinical orbital score greater than 3 and were initially treated for inflammatory Graves’ ophthalmopathy with glucocorticoid therapy. The protocol consisted of 15 mg/kg intravenous injections (with doses up to 1000 mg) of methylprednisolone every fifteen days for two months and then 7.5 mg/kg every two weeks for two months, with additional treatments if necessary. The cumulative dose did not exceed 8 g due to the risk of liver toxicity, as recommended by the EUGOGO working group [6]. Rituximab treatment was initiated when the patients had a visual threat and an optic neuropathy and were considered to be resistant to glucocorticoids. Indications were a threat to visual function or integrity of the cornea, and neuropathy: decrease of visual acuity, visual field defects, severe corneal damage, uncontrolled inflammation. All patients had a proven or suspected optic neuropathy. Patients received one gram of intravenous rituximab in slow infusion, twice, two weeks apart, in combination with 100 mg of intravenous methylprednisolone, 10 mg of Polaramine®, and 1 g of paracetamol. This protocol has already been reported in the literature [13,14].

Efficacy was evaluated based on the evolution of the Mourits’ orbital clinical inflammatory score and on changes of visual acuity or visual field, three to six months after treatment with rituximab. Proptosis and intraocular pressure were also followed. These clinical data were analyzed one month before the patients received rituximab therapy, three to six months after, and at the last follow-up consultation for each patient. The chronology of the treatment protocol for each patient is shown in Fig. 1.

3. Results

The three men and three women of the study all had a thyroidectomy prior to rituximab treatment. One patient did
not stop smoking prior to treatment. Three patients were non-smokers; the other two were ex-smokers. All patients exhibited oculomotor disorders. Visual acuity was abnormal for four patients. The Mourits’ score was greater than or equal to three for five patients. Five patients had proptosis of greater than 18 mm. All six patients had visual field defects. Four patients had emergency decompression surgery (floor and medial wall), which was not sufficiently effective, followed later by a second

Table 1
Description of the six cases treated with rituximab.

<table>
<thead>
<tr>
<th>Case</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>54 years</td>
<td>68 years</td>
<td>53 years</td>
<td>42 years</td>
<td>54 years</td>
</tr>
<tr>
<td>Diagnosis of Graves’ disease/or orbital relapse</td>
<td>March 2011</td>
<td>October 2012</td>
<td>November 2012</td>
<td>August 2011</td>
<td>August 2011</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>At 6 months</td>
<td>At 3 months</td>
<td>At 3 months</td>
<td>At 3 months</td>
<td>At 6 months</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Yes</td>
<td>Non-smoker</td>
<td>Ex-smoker</td>
<td>Ex-smoker</td>
<td>Non-smoker</td>
</tr>
<tr>
<td>Oculomotor disorders</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>NOSPECS</td>
<td>Very severe</td>
<td>Very severe</td>
<td>Very severe</td>
<td>Very severe</td>
<td>Very severe</td>
</tr>
<tr>
<td>Visual field defects</td>
<td>Yes</td>
<td>At 6 months</td>
<td>At 5 months</td>
<td>At 13 months</td>
<td>At 13 months</td>
</tr>
<tr>
<td>Rituximab (time relative to diagnosis)</td>
<td>At 23 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab (time relative to corticosteroids therapy)</td>
<td>13 months</td>
<td>1 month</td>
<td>0 month</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Semi-urgent orbital decompression</td>
<td>At 13 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronal decompression (end of treatment)</td>
<td>At 30 months</td>
<td>At 8 months</td>
<td>At 24 months</td>
<td>At 15 months</td>
<td>At 17 months</td>
</tr>
<tr>
<td>Indication of treatment with rituximab</td>
<td>Decrease of visual acuity and visual field defect</td>
<td>Decrease of visual acuity, visual field defect and corneal involvement</td>
<td>Visual field defect and inflammation</td>
<td>Decrease of visual acuity and visual field defect with compression of optical nerve on imaging</td>
<td>Visual field defect and inflammation</td>
</tr>
</tbody>
</table>
decompression surgery by the coronal approach. The other two patients did not have emergency orbital decompression surgery, but had orbital decompression surgery by the coronal approach at the end of treatment. Patients received Rituximab therapy zero to 13 months after completing corticosteroid therapy. No serious side effects or complications during rituximab therapy were observed (Table 1).

The indication was visual loss in four patients and/or modification of the visual field with the appearance of a central scotoma for at least one eye for all six patients, associated with optic nerve compression on imaging for one patient, severe damage to the corneal surface of one patient, and a persistently high inflammatory score for two patients, despite corticosteroid treatment.

Visual acuity improved in three of four cases and the visual field in four cases (Figs. 2 and 3). The inflammatory score was reduced in three cases. Proptosis decreased in three cases after treatment with rituximab and before orbital decompression by the coronal approach. Intraocular pressure decreased in all six cases.

For case 2, there was limited improvement of visual acuity and visual field after rituximab treatment and surgical orbital decompression. This result may be due to the panretinal
Table 2
Results of the treatment with rituximab on visual acuity, intraocular pressure, corneal lesions, orbital clinical inflammatory Mourits' score, proptosis, and Goldmann visual field.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Visual acuity (decimal, Monoyer far scale and Parinaud near scale)</th>
<th>Intraocular pressure (mmHg)</th>
<th>Cornea</th>
<th>Mourits score (7)</th>
<th>Proptosis (Hertel mm)</th>
<th>Goldmann visual field</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right eye</td>
<td>Left eye</td>
<td>Right eye</td>
<td>Left eye</td>
<td>Right eye</td>
<td>Left eye</td>
</tr>
<tr>
<td>One month before rituximab</td>
<td>2 P10</td>
<td>7 P2</td>
<td>22</td>
<td>26</td>
<td>Punctate keratitis</td>
<td>Punctate keratitis</td>
</tr>
<tr>
<td>Three to six months after rituximab</td>
<td>5 P10</td>
<td>7 P2</td>
<td>22</td>
<td>23</td>
<td>Normal</td>
<td>Punctate keratitis</td>
</tr>
<tr>
<td>Last examination 33 months after treatment</td>
<td>4 P2</td>
<td>5 P2</td>
<td>15</td>
<td>14</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Case 2</td>
<td>One month before rituximab</td>
<td>5 P10</td>
<td>1,5 P14</td>
<td>26</td>
<td>25</td>
<td>Punctate keratitis</td>
</tr>
<tr>
<td>Three to six months after rituximab</td>
<td>1,6 P8</td>
<td>5 P4</td>
<td>12</td>
<td>17</td>
<td>Punctate keratitis</td>
<td>Punctate keratitis</td>
</tr>
<tr>
<td>Last examination 23 months after treatment</td>
<td>1,6 P10</td>
<td>2 P10</td>
<td>13</td>
<td>14</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Case 3</td>
<td>One month before rituximab</td>
<td>Hand motion</td>
<td>1,6</td>
<td>20</td>
<td>20</td>
<td>Punctate keratitis</td>
</tr>
<tr>
<td>Three to six months after rituximab</td>
<td>6 P2</td>
<td>6 P6</td>
<td>16</td>
<td>15</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Last examination 24 months after treatment</td>
<td>12,5 P4</td>
<td>6,3 P2</td>
<td>17</td>
<td>15</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Case 4</td>
<td>One month before rituximab</td>
<td>10 P2</td>
<td>10 P2</td>
<td>23</td>
<td>23</td>
<td>Normal</td>
</tr>
<tr>
<td>Three to six months after rituximab</td>
<td>10 P2</td>
<td>10 P2</td>
<td>12</td>
<td>15</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Case 5</td>
<td>One month before rituximab</td>
<td>1,6 P10</td>
<td>Counting fingers</td>
<td>19</td>
<td>26</td>
<td>Punctate keratitis</td>
</tr>
<tr>
<td>Three to six months after rituximab</td>
<td>3 P8</td>
<td>0,5 P10</td>
<td>14</td>
<td>14</td>
<td>Punctate keratitis</td>
<td>Punctate keratitis</td>
</tr>
<tr>
<td>Last examination 39 months after treatment</td>
<td>6 P2</td>
<td>1,6 P10</td>
<td>14</td>
<td>14</td>
<td>Normal</td>
<td>Punctate keratitis</td>
</tr>
<tr>
<td>Case 6</td>
<td>One month before rituximab</td>
<td>10 P2</td>
<td>10 P2</td>
<td>20</td>
<td>18</td>
<td>Punctate keratitis</td>
</tr>
<tr>
<td>Three to six months after rituximab</td>
<td>10 P2</td>
<td>10 P2</td>
<td>17</td>
<td>17</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Last examination 23 months after treatment</td>
<td>20 P2</td>
<td>16 P1,5</td>
<td>20</td>
<td>17</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
4. Discussion

Rituximab therapy was beneficial in second intention for the six patients in this study, based on three criteria, who had severe ophthalmopathy with inflammatory signs resistant to corticosteroids, decreased visual acuity and/or visual field defects. Anti-CD20 treatments have made it possible to exploit the role of B cells in autoimmunity to treat a number of diseases. B lymphocytes not only produce autoantibodies, but also activate CD4+ T cells, thus playing a role in inflammation. They are also important antigen presenting cells [15]. The CD20+ marker, the target of rituximab, is present during all stages of B cell maturation [16].

Several other non-validated treatment options are also being studied for the treatment of severe Graves’ ophthalmopathy, such as cyclosporine [17] or anti-TNFα.

Rituximab has been used to treat non-Hodgkin lymphoma and autoimmune pathologies such as rheumatoid arthritis and cases of Graves’ ophthalmopathies which are resistant to corticosteroid treatment.

It is generally well tolerated, but patients should be monitored for signs of intolerance or infection. This biotherapy must also be used with caution because of the resurgence of tuberculosis in developed countries [18]. Rituximab affects pro-inflammatory cytokine production and lymphocyte infiltration, but has no effect on the level of autoantibodies as demonstrated by Vannucchi et al. [19] and by El Fassi et al. [12].

Rituximab has been used to treat 43 patients for Graves’ ophthalmopathies in uncontrolled studies resulting in inactivation of the inflammatory phase of the disease in 91% of cases, as reported in the literature up to 2014 [20]. Proptosis and diplopia also improved after treatment in most cases [20]. Proptosis decreased in three of our patients. However, all patients required muscle surgery, in agreement with the results of the series of Khanna et al. [10]. This level of efficiency has been demonstrated in long-term monitoring of a small group of patients [21].

A double-blind randomized study, published in 2014, comparing 31 patients treated with intravenous methylprednisolone or rituximab showed a significantly greater decrease of the inflammatory score in the rituximab group after 16 weeks of treatment. The patients exhibited improved oculomotor limitation and a reduction in the frequency of inflammatory relapses, but no significant improvement in proptosis [22]. The authors suggest that the use of lower doses of rituximab, 500 instead of 2000 mg, decrease the risk of complications, but have the same anti-inflammatory effect. Another study, that compared rituximab to a placebo, did not find a benefit for rituximab in reducing the inflammatory score [23]. However, the therapeutic window for intravenous corticosteroids was four weeks before rituximab therapy in this study, while it was three months for the previous one. This raises the question of the appropriate time to consider rituximab therapy in cases of corticosteroid resistance, when visual acuity and the visual field continue to deteriorate and the inflammatory score does not improve. In our series, this period was between 0 and 13 months. These last two published studies have the limitation that they did not examine the benefit of rituximab on optic neuropathy, which is a major problem and negatively affects the visual prognosis in severe ophthalmopathies. It has been effective on optic neuropathy in some cases [7,10,24], however, it is non-recommended in the last guidelines in 2016 because of the development of optic neuropathy after a rituximab treatment in some cases [6].

Rituximab has also been tested on relapsing Graves’ disease of average severity, independently of any effects on the eyes, demonstrating an increase in TSH and a decrease in T4, up to 27 months after treatment. We have not been able to study this in our series as all patients underwent total thyroidectomy prior to rituximab therapy [25].

The positive results of our study must be balanced by the fact that four patients had initial emergency orbital decompression surgery (by collapse of the lateral and medial orbital walls) prior to rituximab therapy and all had final orbital decompression surgery by the coronal approach after rituximab therapy, during the follow-up period. Surgical removal of the lateral wall and collapse of the medial wall probably also helped to improve symptoms. However, surgery does not decrease lymphocyte infiltration of the orbit, in contrast to rituximab, as discussed by Salvi et al. [24]. We must also consider the fact that our patients received treatment by multiple intravenous injections of corticosteroids prior to being treated with rituximab, which prevents an assessment of the effectiveness of rituximab alone. However, Salvi et al. [22] have reported efficacy of rituximab to lower the inflammatory score when only 19% of the patients in their study received another prior anti-inflammatory treatment.

Rituximab suffers from the lack of a large controlled study against the standard treatment. The study of Salvi et al. [14,22] on 16 patients treated with rituximab versus 16 patients treated with corticosteroids reported superiority of rituximab for the inflammatory score and equivalence for proptosis. Validation of this result on larger cohorts, may lead more clinicians to use rituximab to treat severe inflammatory ophthalmopathies.

5. Conclusion

We successfully used rituximab to treat Graves’ ophthalmopathies without significant side effects resulting in improvement of the symptoms of patients who responded inadequately to corticosteroids, however some patients had orbital decompression shortly before treatment by rituximab. We had positive results on patients with visual threat and optic neuropathy, combined or not with an initial surgical orbital decompression. The description of cases treated with rituximab in centers caring for patients with Graves’ ophthalmopathies may allow a standardized management protocol for all European centers.

Disclosure of interest

The authors declare that they have no competing interest.
References


