Resumen

Objetivo: Evaluar la efectividad y seguridad del tratamiento con rituximab en pacientes con púrpura trombocitopenica y anemia hemolítica autoinmune.

Método: Se han revisado las historias clínicas de los pacientes que iniciaron tratamiento con rituximab como uso compasivo en el año 2004 a dosis de 375 mg/m² semanal durante 4 semanas. Se evaluó la tasa de pacientes que alcanzó respuesta completa según los mejores criterios encontrados en la bibliografía. Se recogieron las reacciones adversas descritas en la historia clínica.

Resultados: Seis pacientes con púrpura trombocitopenica autoinmune fueron candidatos a tratamiento. Cinco iniciaron tratamiento, cuatro de ellos completaron el tratamiento, de los cuales tres obtuvieron respuesta completa. Dicha respuesta es alcanzada en diferentes tiempos y es mantenida al menos durante 6 meses. Dos pacientes con anemia hemolítica autoinmune fueron tratados y ambos alcanzaron respuesta completa también en diferentes tiempos y esta se mantuvo al menos durante 8 meses. Las reacciones adversas al tratamiento que sufrió algún paciente fueron leves.

Conclusiones: Rituximab es una nueva expectativa al tratamiento de citopenias autoinmunes refractarias, con un buen perfil de seguridad.


Summary

Objective: To evaluate the efficacy and safety of treatment with rituximab in patients presenting autoimmune thrombocytopenic purpura and haemolytic anaemia.

Method: A check was carried out of the medical records of the patients starting treatment with rituximab for compassionate use in 2004 at doses of 375 mg/m² per week for 4 weeks. The rate of patients achieving full response in accordance with the best criteria found in the bibliography was assessed. All adverse reactions described in the medical records were gathered.

Results: Six patients with thrombocytopenic purpura were candidates for treatment. Five began treatment, four of them completed treatment, and three of these patients achieved full response. This response was achieved at different times and was sustained for at least six months. Two patients with autoimmunne haemolytic anaemia were treated and both achieved full response again at different times and in this case, it was sustained for at least 8 months. One patient suffered mild adverse reactions to treatment.

Conclusions: Rituximab is a new perspective for the treatment of refractory autoimmune cytopenias, and has a good safety profile.

Key words: Rituximab. Autoimmune haemolytic anaemia. Thrombocytopenic purpura. Compassionate use.

INTRODUCTION

Autoimmune thrombocytopenic purpura (ATP) and autoimmune haemolytic anaemia (AIHA) are autoimmune haematological alterations characterised by premature cell destruction mediated by antibodies in the reticuloendothelial system.

ATP is characterised by persistent thrombocytopenia (peripheral blood platelet count < 150 x 10⁹/l) and generally by mucocutaneous hemorrhagic syndrome⁴⁻¹⁰. The
acute presentation of the disease takes place in children and is usually preceded by viral infection; its hemorrhagic manifestations are abrupt and remit spontaneously. In adults, it presents recurrently with mild to serious hemorrhagic manifestations in the skin, mucous or gums. Annual incidence is of 5.8-6.6 cases/100,000 inhabitants.

AIHA includes a heterogeneous group of processes characterised by the early destruction of the red blood cells induced by antibodies against the membrane. It has a prevalence of 1-3 cases/100,000 inhabitants. According to the type of antibody, it may be classified into AIHA of the warm antibody type (IgG) aimed at one of the Rh antigens or AIHA of the cold antibody type (IgM) which act against antigens related with the erythrocyte membrane.

Both pathologies (ATP and AIHA) respond normally to treatment with corticoids, the indicated frontline treatment. As a second choice, splenectomy is recommended, which is effective in 60-70% of cases and later, if there is no response or if there is a relapse, treatment with immunosupressing agents (danazole, vincristine, cyclophosphamide, azathioprine, cyclosporine A) or intravenous immunoglobulins (IGIV) is administered. These have proved to be temporarily effective in increasing the platelet count, though no consensus exists as to the choice of treatment in these refractory cases.

The complexity and refractivity of the treatments and the chronicity of the disease have brought about research into new therapies such as monoclonal antibodies, which have been used in other autoimmune diseases in order to modify the immunological response. Rituximab is a murine/human chimeric monoclonal antibody that specifically binds to the CD20 membrane antigen of the normal and malignant B-lymphocytes (but not to the hematopoietic progenitor cells), due to its Fab domain. At the same time, the Fc domain establishes lysis function by means of cytotoxicity, and furthermore the bond with the antigen induces the death of the cells through apoptosis. The treatment of these autoimmune pathologies with rituximab requires authorisation by the Ministry of Health for compassionate use.

The aim of this paper is to analyse the effectiveness and safety of the treatment of ATP and AIHA at a single centre in 2004.

METHOD

A retrospective study was carried out in which applications for the compassionate use of rituximab were checked for the year 2004. Data were collected for the patients who were authorised treatment with rituximab for ATP and AIHA. Informed consent for this use has the special feature of checking the patient’s awareness of a serious adverse reaction known as cytokine release syndrome.

These patients’ medical histories were studied, and the following data were collected: age and sex, diagnosis, dosage, previous treatment, clinical evolution and side effects. The dosage of rituximab was 375 mg/m² per week over four weeks.

The following were considered as response criteria: For ATP (Table I), the increase in platelets achieved after at least two weeks of administering the last dose of rituximab. Although there are some discrepancies, the most accepted classification is that proposed by Stasi who sets the limit for full response at 100,000 platelets/mm³. For AIHA (Table II), the concentration of haemoglobin at least one month after administering the last dose of rituximab. Another additional response criterion is a negative outcome in the Coombs test.

### Table I. Response criteria for ITP

<table>
<thead>
<tr>
<th>Type of response</th>
<th>Increase in platelet recount/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>&gt; 100,000/mm³</td>
</tr>
<tr>
<td>Partial response</td>
<td>50-100,000/mm³</td>
</tr>
<tr>
<td>Minimum response</td>
<td>30-50,000/mm³</td>
</tr>
<tr>
<td>No response</td>
<td>&lt; 30,000/mm³</td>
</tr>
</tbody>
</table>

### Table II. Response criteria for AIHA

<table>
<thead>
<tr>
<th>Type of response</th>
<th>Increases in haemoglobin levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>≥ 1.5 g/dl compared to the concentration before treatment and the c.c. HgL &lt; 10 g/dl without need for transfusion at least one month before completing treatment Negative result in direct Coombs’ test</td>
</tr>
<tr>
<td>No response</td>
<td>&lt; 1.5 g/dl compared to the concentration before treatment if the haemoglobin concentration levels are &lt;10 g/dl No negative result in direct Coombs’ test</td>
</tr>
</tbody>
</table>

RESULTS

Autoimmune thrombocytopenic purpura

Compassionate use of rituximab was requested for six patients. It was only administered in five of them (three males and two females). Patients’ mean age was 66. Three patients were diagnosed with idiopathic ATP, 1 presented ATP associated with B-CLL and another was diagnosed with Evans syndrome (ATP+AIHA) although treatment was motivated by the symptomatology associated with ATP.

Prior to treatment with rituximab, patients had received multiple treatment regimens. All included steroids and IGIV (four of them danazole and two immunosupressing agents such as vincristine, azathioprine, cyclosporine, methotrexate). Only one patient was splenectomised. The average number of previous treat-
ments received was 4. The figures for platelets for patients prior to the start of treatment oscillated between 1,000 and 29,000/mm³.

Rituximab was administered at doses of 375 mg/m² per week over four weeks. One patient only received the first dose because he died due to causes unrelated to treatment, the remaining four (83.3%) received full treatment. Patients received rituximab associated with other treatments (corticoids in four patients and danazol in another).

Of the four patients receiving the full treatment, three (75%) obtained full response and the only patient who was splenectomised did not respond to treatment during the eight weeks after the last dose of rituximab, and hence it was decided to recommence monthly treatment with immunoglobulins.

As for the three patients who achieved full response, two of them did so in the first week of treatment achieving platelet figures of 100,000/mm³ and 107,000/mm³ respectively. However, the third patient responded later reaching a minimum response three weeks after the end of treatment, a partial response at five weeks and full response at twelve weeks after the last dose had been administered.

The three patients achieved platelet counts of above 100,000/mm³ and two of them even achieved concentrations of over 150,000/mm³ reaching figures of 269,000/mm³ and 203,000/mm³ respectively.

At six months after the end of treatment, two patients sustained full response and at 16 months, one presented partial response and received treatment with corticoids and the other patient (the one who responded later) continues to present full response two years after the end of treatment, sustaining platelet figures of 131,000/mm³ with no additional treatment required.

All patients presented good tolerance to treatment with no significant adverse effects being observed.

Autoimmune haemolytic anaemia

Compassionate treatment was authorised for two patients. The first of these was a sixty-six-year-old, non-splenectomised male, previously treated with chlorambucil to treat chronic lymphocytic leukemia and steroids when presenting with episodes of AIHA. He had also been treated previously with cyclophosphamide, vincristine and prednisone on a monthly basis receiving eight cycles. Later he presented with new episodes of AIHA and so it was decided to administer monthly treatments with rituximab (375 mg/m²), cyclophosphamide (750 mg/m²) and dexamethasone (12 mg for 7 days) receiving 6 doses. The concentration of haemoglobin at the start was 11.6 g/dL and he presented direct, positive Coombs test results. Following treatment, the patient achieved full response with haemoglobin of 13.7 g/dL. Response began 6 weeks after the start of treatment and full response was achieved at 12 weeks. Two months after administering the last cycle, direct Coombs test became negative and at eight months, full response was sustained with hemoglobin reaching 13.7 mg/dL.

Between the second and third cycles, the patient presented with diarrhea, abdominal pain and fever developing over 5 days, which was resolved without problems.

The second patient was a sixty-nine-year-old, non-splenectomised male whose diagnostic was associated with B-CLL treated with fludarabine and steroids. He presented direct, positive Coombs test and the concentration of haemoglobin at the start was 8.3 g/dL. He was treated with rituximab at doses of 375 mg/m², cyclophosphamide (750 mg/m²) and dexamethasone (12 mg for 7 days). Having received two doses, hemoglobin concentration rose to 11.2 g/dL achieving full response. At six months after treatment, he presented with haemoglobin concentration of 14.1 g/dL and at 12 months, 15.4 g/dL together with negative Coombs test. The patient suffered a slight reaction which remitted with hydrocortisone and a decrease in infusion speed, with no need to suspend treatment.

**DISCUSSION**

Full response to the treatment of ATP with rituximab described in the bibliography is around 50% and the sustained response after 10–18 months post-treatment is described as being between 25 and 30% of patients. In accordance with these results, 75% of our patients with ATP treated with rituximab achieved full response after treatment. The time it takes to reach full response is variable, with late responses being observed. Sustained response was observed in all patients even one year after treatment in two patients (50%). No noteworthy adverse reactions were observed either during treatment or one year after.

Rituximab in AIHA also seems to be effective in AIHA associated with lymphoproliferative syndromes. At doses of 375 mg/m² per week over 4 weeks, full remission is achieved according to the literature of some 40%, and is sustained over 15–22 months after treatment without finding severe adverse effects or derived infections, presenting a good safety profile. One hundred per cent of our patients with AIHA associated with lymphocyte pathologies achieved full response. The time needed to achieve full response varies from 2 to 6 weeks. In the short term, this treatment did not present any serious adverse effects.

Despite the fact that these alterations have a physiopathology that has been known about for over 50 years, therapeutic regimes are based on experts’ opinions. The literature lacks clinical tests to allow more rational therapy, to find out its evolutionary indicators or pronostics, to define predictive response factors and response duration, the optimal dosage and administration and the implication of the use of combined therapies.
The effectiveness of rituximab in refractory autoimmune thrombocytopenic purpura and haemolytic anaemia

References