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ORIGINAL ARTICLE

Francisco Javier Peñalver · Victor Jiménez-Yuste · Manuel Almagro · Alberto Alvarez-Larrán · Lluis Rodríguez · Marisol Casado · Laura Gallur · Pilar Giraldo · Roberto Hernández · Dolores Menor · Maria José Rodríguez · Dolores Caballero · Raúl González · José Mayans · Isabel Millán · José Rafael Cabrera · On behalf of the Multi-institutional Retrospective Spanish Study on the use of rituximab in refractory ITP

Rituximab in the management of chronic immune thrombocytopenic purpura: an effective and safe therapeutic alternative in refractory patients

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Abstract Rituximab induces B-cell depletion; therefore, it has been used in the treatment of immune thrombocytopenic purpura (ITP). The aim of this retrospective study was to evaluate the effectiveness of rituximab in the treatment of 89 patients with chronic ITP refractory to several treatments. All the patients had platelet counts $<30\times10^9$/l. They had received a median of five (2–13) previous treatments, and 47 had undergone splenectomy. Rituximab was administered i.v. at 375 mg/m^2 in four weekly doses in 77 patients, and 12 patients received 1–6 doses. Forty-nine patients (55.1%) reached platelet counts $>50\times10^9$/l; 41 (46%) achieved a complete response (CR; platelets $>100\times10^9$/l), and eight (9%) obtained a partial response (platelets $50–100\times10^9$/l). Overall, 31 patients (35%) maintained response, including 15 patients in whom splenectomy failed, with a median follow-up of 9 months (2–42), 12 for more than 1 year. The unique predictor of a maintained response was to reach a CR. Heavily treated patients (more than three different previous treatments, including any corticosteroids) and those with longer ITP duration (>10 years from diagnosis) had a worse response. Non-splenectomized patients had a better early response rate than those splenectomized. Rituximab was well tolerated, with two fever episodes following infusion and two reports of skin rash. Rituximab induced clinical responses in multi-treated refractory ITP patients with little toxicity and should be considered as an early therapeutic option in this setting, even as an alternative to splenectomy in selected patients.

Keywords Immune thrombocytopenic purpura · Refractory ITP · Rituximab · Autoimmunity

F. J. Peñalver
Fundación Hospital Alcorcón, Madrid, Spain

V. Jiménez-Yuste
Hospital La Paz, Madrid, Spain

M. Almagro
Hospital Virgen de las Nieves, Granada, Spain

A. Alvarez-Larrán
Hospital Clinic, Barcelona, Spain

L. Rodríguez
Hospital Germans Trias y Pujol, Badalona, Spain

M. Casado
Hospital Infanta Cristina, Badajoz, Spain

L. Gallur
Hospital Vall D` Hebron, Barcelona, Spain

P. Giraldo
Hospital Miguel Servet, Zaragoza, Spain

R. Hernández
Hospital de Txagoritxu, Vitoria, Spain

D. Menor
Hospital de Getafe, Madrid, Spain

M. J. Rodríguez
Hospital Universitario de Canarias, Tenerife, Spain

D. Caballero
Hospital Clínico de Salamanca, Salamanca, Spain

R. González
Hospital Sant Joan, Alicante, Spain

J. Mayans
Hospital Arnau de Vilanova,
Valencia, Spain

I. Millán
Biostatistics Department,
Clínica Puerta de Hierro, Madrid, Spain

J. R. Cabrera (✉)
Hematology Department,
Hospital Universitario Puerta de Hierro,
San Martin de Porres 4,
28035 Madrid, Spain
e-mail: jrcabrera@aehh.org
Tel.: +34-91-3445598
Fax: +34-91-3730535

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by platelet destruction mediated by autoantibodies reacting against platelet antigens, which causes their premature destruction by the reticuloendothelial system and particularly by the spleen [2, 4, 15]. ITP usually presents as isolated thrombocytopenias and idiopathic ITP, but in some cases, autoimmune thrombocytopenias develop in the course of a lymphoproliferative disorder, more frequently chronic lymphocytic leukaemia (CLL), B-cell non-Hodgkin lymphoma (NHL) or a systemic immune disease [20].

In the treatment of ITP, corticosteroids are the main therapeutic option, followed by intravenous immunoglobulin (IVIG) and/or other immununosuppressants, and then by splenectomy. If these modalities are not successful, danazol and chemotherapy reagents such as cyclophosphamide and vincristine can be employed but are less frequently used [2, 13]. Approximately 30–35% of the patients do not respond to therapy, even to splenectomy, which bears some risk specially for patients with advanced age, comorbidities and other risk factors, making it necessary to find other effective therapeutic options [7, 13, 15].

Rituximab is a chimeric murine/human monoclonal antibody against the CD20 antigen on B lymphocytes. Rituximab induces a targeted B-cell depletion [6, 9, 11, 20], and its use in chronic ITP [6, 14, 15, 18], autoimmune haemolytic anaemia [21] and other autoimmune diseases [18] is based on the attempt to eliminate autoreactive B-cell clones.

It is difficult to perform randomized clinical trials in chronic ITP patients that do not respond to usual or current therapies due to the lack of patients and the need to perform these studies as worldwide multi-centre initiatives. Previous results with rituximab in chronic ITP globally including 144 patients indicate that it is effective in nearly 50% of them, with a complete response rate of 34%, a duration of response up to 27 months and more than 40% recurrences [16, 18, 20]. Therefore, controlled studies that include larger numbers of patients that have received several treatments in different clinical situations (splenectomy or not, associated diseases etc.) are necessary to assess the role of rituximab in the treatment of these patients with few therapeutic alternatives.

In this report, we present the results of a retrospective multicentric Spanish study designed to assess the therapeutic efficacy and toxicity of rituximab in chronic ITP patients unresponsive to several treatments.

Patients and methods

We have performed a retrospective multicentric analysis of chronic ITP patients treated with rituximab between April 2001 and March 2004 in Spain. Patients' data were obtained with a questionnaire that was submitted to the participating centres and was filled out by the physician. We received questionnaires from 43 centres. Collected data included age, sex, diagnosis, date of diagnosis, comorbidities, previous treatments for ITP, platelet counts before rituximab, response to treatment, and duration of response and rituximab toxicity.

Inclusion criteria

In the present study, we have included patients with immune thrombocytopenia, both idiopathic ITP and immune thrombocytopenias associated with lymphoproliferative and autoimmune diseases.

Refractory ITP patients were eligible for treatment with rituximab. We defined as refractory ITP those patients with $<30\times10^9$/l platelets prior to rituximab treatment and that had received at least two therapy lines before rituximab. All patients gave informed consent to receive the rituximab under off-label conditions. This study was approved by the local ethics committee, and informed consent for analysing patients' data was obtained.

Exclusion criteria

We have excluded patients with thrombocytopenia secondary to a shortened survival and/or decreased production of platelets, like drug-induced thrombocytopenia, myelodysplastic syndromes, chronic liver diseases, human immunodeficiency virus (HIV) infection and other viral infections.

Treatment

Patients received rituximab (Mabthera; Roche Farma, Spain) 375 mg/m^2 per week intravenously for 4 consecutive weeks. During the initial period, 31 patients with platelet counts less than 10×10^9/l and/or bleeding received rituximab with other therapy, either corticosteroids (20 of 31 patients), corticosteroids and IVIG (3 of 31 patients), IVIG (2 of 31 patients) or other treatments they were previously receiving (6 of 31 patients).

Response criteria

Platelet counts were evaluated both at the initial and the maximum response. The response criteria were a modification of those published by Stasi et al. [14], as follows: complete response (CR), platelets $>100\times10^9$/l; partial response (PR), $50–100\times10^9$/l; minimal response, $30–50\times10^9$/l. Patients with platelet counts lower than 30×10^9/l were considered non-responders.

Statistical analysis

Analysis of the data was primarily descriptive, using percentages, mean values and standard deviations, medians

and ranges as required. Chi-squared test was used to compare proportions and Student's *t* test to compare means. We have also represented the results with graph bars including means and 95% confidence intervals (CI) and box plots with percentiles and extreme values.

Results

The patients' clinical characteristics are presented in Table 1.

Pretreatment characteristics

Prior to rituximab, the patients had received two or more treatments, with a median of 5 (range 2–13). These included corticosteroids (98%), IVIG (88%), danazol (36%), cyclosphosphamide (26%), cyclosporine (17%) and anti-D immunoglobulin (15%). Forty-seven patients (53%) had undergone splenectomy. Splenectomized patients had received a median of seven treatments (3–13) before rituximab.

The lowest platelet counts before treatment were 1×10^9/l, with a median platelet count of 8×10^9/l (range 1–30); 66.3% (59) of the patients had platelet counts below 10×10^9/l.

The median time from diagnosis of ITP to rituximab therapy was 31 months (range 1–305). Overall, 87% (77 of 89) patients received four doses of rituximab, and 13% (12 of 89) patients received between one and six doses.

Table 1 Patients' characteristics

Number of patients	89
Sex	
Female	51 (57%)
Male	38 (43%)
Age (years)	
Median	56
Range	4–98
Duration of ITP to rituximab therapy (months)	
Median	31
Range	1–305
Splenectomy	47 (53%)
Number of previous treatment	
Median	5
Range	2–13
Median number of platelets ($\times10^9$/l) (range)	8 (1–30)
Associated disease	
Idiopathic	58 (65.3%)
Evans syndrome	6 (6.7%)
CLL	14 (15.7%)
AD	9 (10.1%)
NHL	2 (2.2%)

CLL Chronic lymphocytic leukaemia, *AD* autoimmune disease, *NHL* non-Hodgkin lymphoma

Response to treatment and its characteristics

Forty-one patients (46.1%) achieved CR and eight patients (9%) obtained PR, with an overall rate (OR) of 55.1% (49 out of 89) (Fig. 1).

A large proportion of responses took place in the first week of treatment (40% of the responders, 20 patients) (Fig. 2). During the first 5 weeks, 52% of the patients and 87% of the responders achieved response. We also found two late responses, appearing 21 and 44 weeks after the first infusion. The patient who responded at week 21 achieved a CR that persisted after 9-month follow-up. The patient who responded 44 weeks after infusion only achieved a PR that was maintained at least for 3 months.

Maximum response was achieved after a median time of 5 weeks, with median platelet counts of 141×10^9/l (Fig. 3).

Response maintenance

Overall, 55.1% (49 of 89) of the patients receiving rituximab reached platelet counts of more than 50×10^9/l. The response was maintained in 35% (31 of 89) of patients, with a median follow-up of 9 months (2–42) and, in 12 patients, for more than 1 year. Moreover, 63% (31 of 49) of the patients with OR and 73% of those with CR (30 of 41) were able to maintain it (Fig. 4). One patient with PR also maintained response.

Factors associated with response

Non-splenectomized patients had a better early response rate than splenectomized patients. The OR rate in non-splenectomized patients was 67% (CR 50%, 21 of 42; PR 17%, 7 of 42) vs 44.7% OR (CR 42.6%, 20 of 46; PR 2.1%, 1 of 46) in the splenectomy group (p=0.029). However, there were no differences in maintained re-

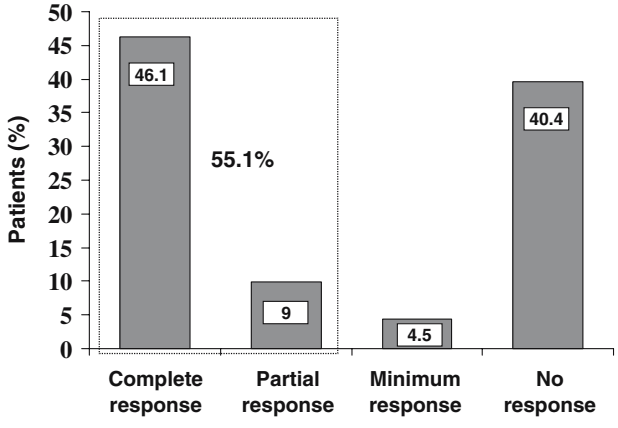

Fig. 1 Response to rituximab therapy: 41 patients achieved a CR (46.1%) and 8 patients obtained a PR (9%). Overall, 49 patients (55.1%) obtained OR (platelets $>50\times10^9$/l)

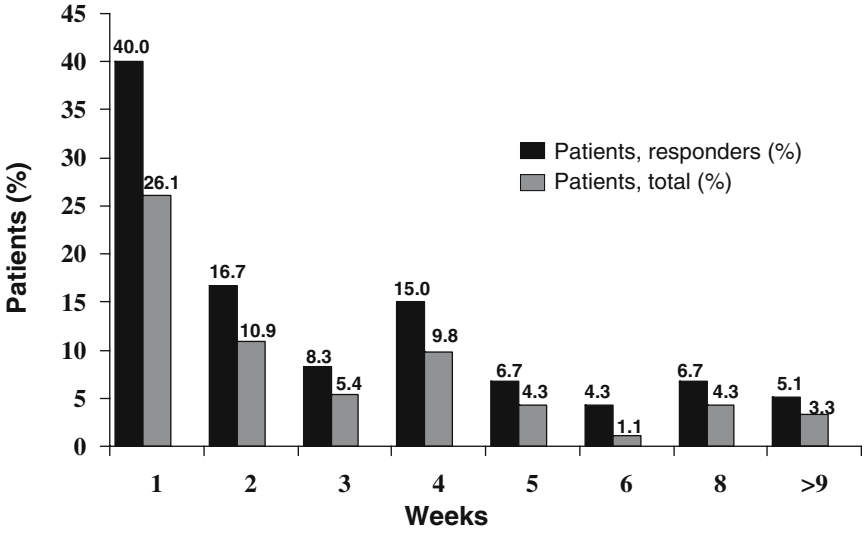

Fig. 2 Timing of response to rituximab therapy. The majority of responses took place in the first week (26.1% out of the total, 40% out of the responders). During the first 5 weeks, 52% of the patients and 87% of the responders reached response

sponse rates between the two groups (38 and 32%, respectively) (p=0.815).

Heavily treated patients before rituximab therapy (more than three different treatments, including any corticosteroids) did worse in terms of response rate than those receiving fewer treatments. Non-response rate of heavily treated patients (85% of the whole series) was 45%, while non-response rate of lightly treated patients was 23% (p=0.012). Both groups showed similar CR rates, 49 vs 46% for heavily and lightly treated patients, respectively. Therefore, we can attribute the differences in the OR to a higher rate of PR in the latter group (31 vs 5%).

Those patients with longer duration of ITP (>10 years) had a worse response to rituximab. Only 37.5% of patients in this group achieved platelet counts of more than 50×10^9/l, compared to 65.2% of the patients with ITP lasting less than 10 years (p=0.043). Nevertheless, we found no statistically significant differences between both groups in the maintenance of the response.

There were no differences in the response rate between patients treated with rituximab alone (CR 47.4%) or in combination with other therapies (CR 45.2%). Similarly, there were no differences in the percentage of maintained response between these two groups (35.7 and 35.5%, respectively) (p=0.959).

Eighty-seven per cent of the patients received four doses of rituximab. Twelve other patients received between one and six doses of rituximab (eight patients, three doses; two patients, five doses; and one patient, six doses and only one dose each). In this group, it was observed that four maintained CR (3 patients that had received three doses and 1 patient that have received one dose). Age and gender did not seem to influence response to rituximab therapy. Fifty-eight per cent of the men (n=38) and 53% of the women (n=51) responded (p=0.843). We did not find any significant differences in the maintained response rates between patients with and without associated diseases (idiopathic,

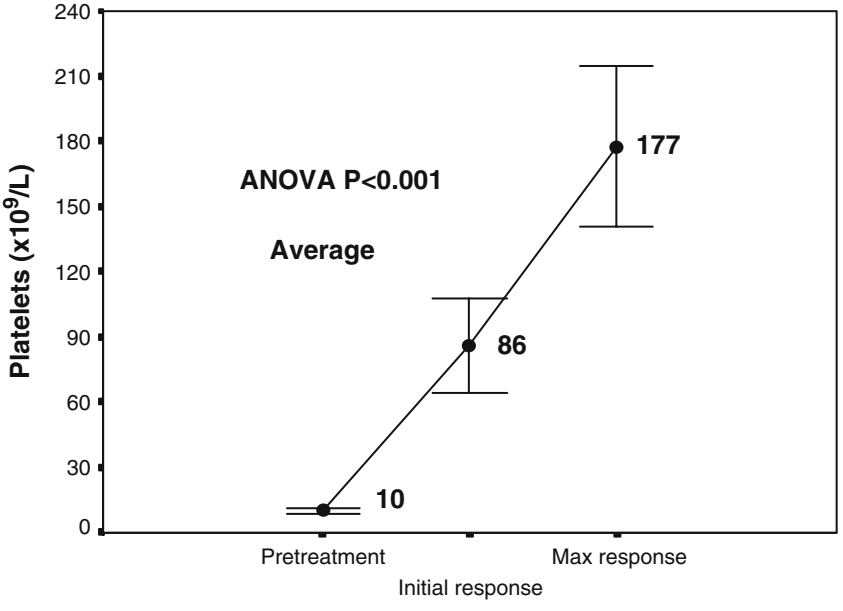

Fig. 3 Platelet counts prior to treatment, at the beginning and at maximum response

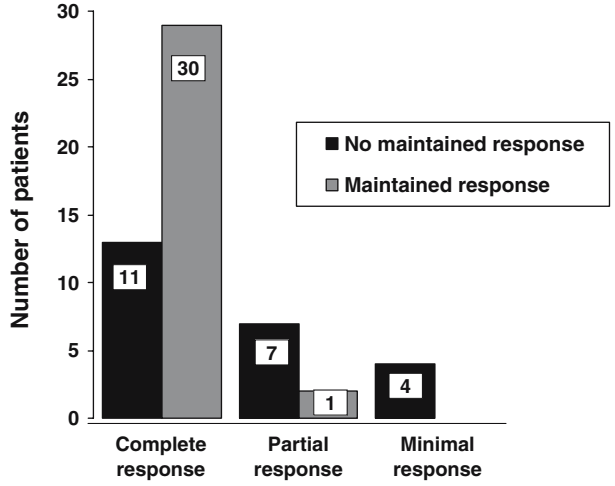

Fig. 4 Maintenance of response. The response was maintained in 31 patients (35%), with a median follow-up of 9 months; 30 patients (73% of those with CR) were able to maintain their response

Evans syndrome, CLL, NHL and autoimmune diseases) (Fig. 5).

Toxicity and side effects

The toxicity of the treatment with rituximab was minimal. Immediate side effects were two fever episodes during infusion and transitory rash in two cases. No infectious complications were communicated.

Discussion

This study aimed to describe the characteristics of response to rituximab in 89 patients with chronic ITP refractory to several treatments. To the best of our knowledge, this series is the largest reported to date on the use of rituximab in chronic ITP. Our results show that rituximab induces a clinically significant response in severe chronic ITP unresponsive to other therapeutic options. We have even seen responses in splenectomized patients, a subgroup of patients in whom other curative therapies are not readily available. In this series, non-splenectomized patients showed higher response rates. Splenectomy did not negatively influence the maintained response rate, but the rate of early responders in this group was smaller. These results seem to confirm the hypothesis that an intact spleen might be necessary to achieve early responses, and this would explain the better initial responses seen in non-splenectomized patients that do not result in differences in the maintained response rates.

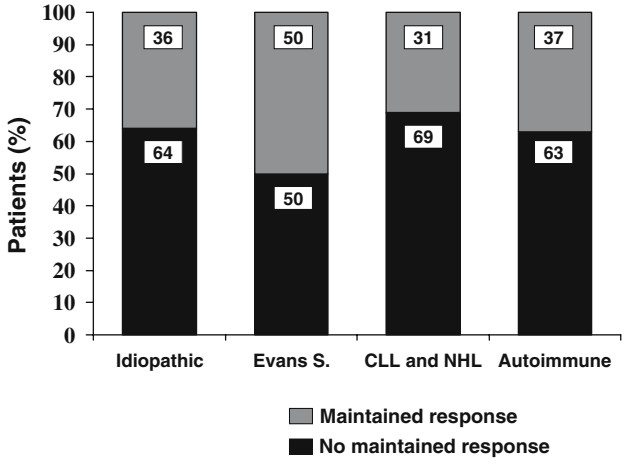

Fig. 5 Associated diseases and maintained response. There were no significant differences in a maintained response between the patients with associated diseases. *CLL* Chronic lymphocytic leukaemia, *NHL* non-Hodgkin lymphoma

Splenectomy is traditionally considered the second-line treatment for relapsed ITP. About 65% of patients who undergo splenectomy achieve a complete remission [7, 8, 13, 15, 17], but splenectomy is an invasive procedure with potential risks and with a relatively large rate of complications [7, 8, 10, 12, 13, 15], mainly in older patients. Rituximab could replace splenectomy as a second-line treatment for ITP. It shows an excellent tolerability and a minimal toxicity and achieves maintained responses in one third of the patients, with evidences of extremely long-lasting responses [5]. Repeated treatment results in further response [14]. It has been useful for children, adolescents [1, 16, 19] and older patients with a good tolerance.

This report also includes cases of refractory ITP associated with CLL (14 cases) and NHL (two cases), which were excluded in other reports [13, 14]. We did not find any statistically significant differences in the maintained response rate between these patients and those with idiopathic refractory ITP. This fact leads us to think rituximab behaves as an immunosuppressor in refractory ITP independent of the cause of this autoantibody-mediated disease.

Achievement of a CR seems to be the best predictor of a maintained therapeutic response; in our series, 73% of the patients with a CR maintained it. Our findings show that the response is not influenced either by platelet counts prior to treatment or by the gender or age of the patient, in contrast to other reports [14, 20]. So far, no pretreatment laboratory parameters predicting response have been identified [6, 20].

It has been suggested that in patients previously treated for long periods of time with different immunosuppressive drugs, rituximab probably can be less effective, besides causing damage in these heavily treated patients [18]. Nevertheless, our results indicate that rituximab can induce good responses even in heavily treated refractory ITP patients and that it could be a good option as a second line of therapy, previous to splenectomy.

The optimal rituximab dosing scheme in autoimmune diseases has not been established. In all reported series, the therapeutic scheme for ITP patients included four weekly doses of 375 mg/m^2 of rituximab. In our series, 12 patients (13%) received other schemes with 1–6 doses of rituximab without clear differences in the responses. Similar results

have been recently published in childhood chronic ITP patients treated with a single dose of rituximab [16]. Most responses in our series appeared after the first dose. A single dose could be enough in some cases, especially in non-splenectomized patients. In Taube's report, none of the splenectomized patients (3 of 22) reached response with a single dose of rituximab. Probably, these patients would need higher doses of rituximab to achieve response.

Rituximab induced rapid responses, most of which took place in the first week of infusion. Early responses are likely to be mediated by opsonized B cells that block Fc receptors in the reticuloendothelial system. This is a similar mechanism of action to that described for IVIG and anti-D immunoglobulin [3].

The obtained response can be attributed to rituximab because there is a temporal relationship between rituximab infusion and response. Eighty-seven per cent of the responses appeared in the first 5 weeks after initiation of therapy. Moreover, these responses seemed to be unaffected by the fact that 31 patients received other drugs together with rituximab, mainly corticosteroids, therefore confirming rituximab as the main factor responsible for the therapeutic benefit.

The toxicity of the treatment in our study was minimal, and no infectious processes were communicated. No patient developed neutropenia. Patients receiving rituximab for refractory ITP show minimal adverse effects related to rituximab infusion, which can be easily controlled with usual therapeutic measures [6, 13, 14, 20]. This fact indicates rituximab is rather safe for the management of non-neoplastic autoimmune disease.

In conclusion, rituximab induces a clinical effect not seen with other therapies in ITP patients refractory to several treatments, with little associated toxicity, and it can be considered as an alternative to splenectomy. One third of the patients show maintained responses, and these significant responses are seen even in the most refractory group of splenectomized patients. The therapeutic objective of rituximab in chronic refractory ITP must be CR, as this is the only predictor of a maintained response. Administration schemes must be developed to adjust to the characteristics of autoimmune diseases. Controlled studies must also be conducted to analyse the association with other therapies in order to enhance its therapeutical effect or to lengthen it, and to settle the indication for rituximab retreatment after the first therapy.

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