RIC

ARTÍCULO ORIGINAL

A single-institution, 20-year prospective experience with an affordable Fc-receptor blockade method to treat patients with chronic, refractory autoimmune thrombocytopenic purpura

Roberto Estrada-Gómez,* Olga Vargas-Castro,** Mabel Oropeza-Borges,**
Martha L. González-Carrillo,* Beatriz Pérez-Romano,* Guillermo J. Ruiz-Argüelles*,**

*Laboratorios Clínicos de Puebla.
**Centro de Hematología y Medicina Interna de Puebla.

ABSTRACT

In a 20-year period in a single institution, 34 patients with chronic, refractory autoimmune thrombocytopenic purpura were prospectively treated with ex vivo anti-D opsonized autologous red blood cells. All patients had received previous treatment with steroids and/or immunosuppressive agents, and 11 had been splenectomized. Twenty one patients had an increase in the platelet count; in five cases, the increase was more than 50 x 10^9/L platelets and in 16 the increase was more than 100 x 10^9/L platelets. Early responses were observed in 20 patients and late responses in seven, whereas seven patients (20%) did not respond at all. Nine of the 20 individuals who achieved an ER had a subsequent drop in the platelet count; however, only three had a drop below 50 x 10^9/L. When last censored, of the 34 patients, 24 (70%) had a platelet count above 50 x 10^9/L. The 84-month thrombocytopenia-free (over 50 x 10^9/L platelets) status of the whole group is 70%, whereas the 84-month complete remission (over 100 x 10^9/L platelets) status of the whole group is 50%. It is concluded that the use of ex vivo anti-D opsonized red blood cells may represent another, substantially cheaper treatment of patients with chronic, refractory, autoimmune thrombocytopenic purpura.

Key words. Purpura. Thrombocytopenic. Treatment. Anti-D.

Experiencia prospectiva de 20 años en una sola institución con un método accesible de bloqueo de receptores Fc para tratar a pacientes con púrpura trombocitopénica crónica autoinmune refractaria

RESUMEN

En un período de 20 años tratamos 34 pacientes con púrpura trombocitopénica autoinmune crónica refractaria, con inyección de glóbulos rojos autólogos opsonizados ex vivo *con anti-RhO-D. Todos los pacientes habían fallado a tratamiento previo con esteroides y 11 habían sido sometidos a esplenectomía. En 21 pacientes (62%) se observó incremento en la cuenta plaquetaria: En cinco casos las plaquetas ascendieron más de 50 x 10^9/L y en 16 más de 100 x 10^9/L. Se observaron repuestas tempranas en 20 casos y tardías en siete. En siete pacientes no hubo ninguna respuesta. Se observaron mejores respuestas en mujeres que en hombres, en pacientes menores de 18 años y en pacientes con más de 50 x 10^9/L plaquetas al iniciar el tratamiento. La posibilidad de permanecer con más de 50 o de 100 x 10^9/L plaquetas a 84 meses fue, para todo el grupo de 70% y 50%, respectivamente. Se concluye que el tratamiento con glóbulos rojos autólogos opsonizados con anti-D es útil en algunos pacientes con trombocitopenia crónica refractaria.*

Palabras clave. *Púrpura. Trombocitopénica. Tratamiento. Anti-D.*

INTRODUCTION

Several approaches have been used in the treatment of patients with autoimmune thrombocytopenic purpura (ATP): Corticosteroids, splenectomy, Fc receptor (FcR) blockade, immunoppressive agents, etc.[1-3] The FcR blockade has been accomplished with intravenous (IV) immunoglobulin G (IV-IgG) (2), IV

anti-RhO-(D) IgG (anti-D) (2) or *ex vivo* anti-D opsonized autologous red blood cells (RBC).[4-7] In the last years we have been treating patients with chronic, refractory ATP with *ex vivo* opsonized autologous RBC.[5,6] We report herein our 20-year, single institution prospective experience with this method of FcR blockade.

MATERIAL AND METHODS

Patients

All RhO (D) positive consecutive patients with chronic, refractory ATP studied and treated in the *Centro de Hematología y Medicina Interna de Puebla* since 1987 were prospectively entered in the study; al of them displayed dry purpura (ecchimosis and petechiae). Fifteen had received immunosuppressive agents (13 azathioprine and two mercaptopurine) for periods ranging from two to 27 months, whereas eleven had been splenectomized; a normal bone marrow aspirate was a requisite. The table 1 shows some of the salient data of these individuals.

Treatment

Five mL of a venous blood sample were obtained in sterile tubes containing EDTA-K3.[6,7] Three ml. of saline solution with 100 ug. of anti-RhO (D)-IgG (Cutter) were placed in a sterile flask; 2 mL of the patient's packed RBC were added, the mixture incubated with gentle rotation at 25 ºC for 1 hr and the whole mixture was given slowly in a single IV dose, repeated every other day to a total of six. The patients who did not have an early response were given a single intramuscular delivery of 250 ug of anti-RhO (D)-IgG.

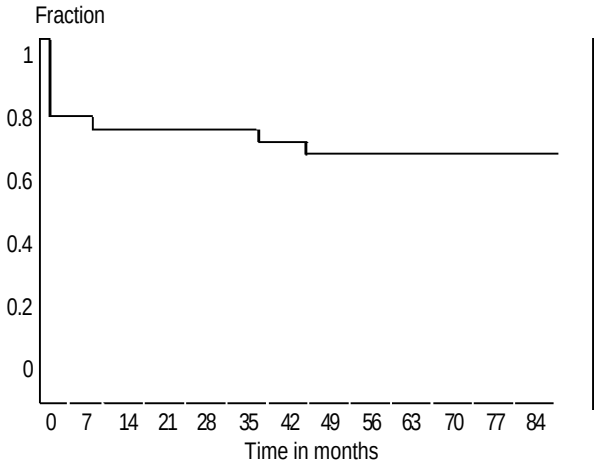

Figure 1. Kaplan Meier curve of the probability of the 34 patients of remaining with more than 50 x 10^9/L platelets after the treatment.

Response criteria

A partial response (PR) was defined as a platelet increase of more than 50 x 10^9/L and a complete response (CR) as an increase of more than 100 x 10^9/L. above the baseline levels. Early response (ER) was defined 24 hr after the last dose of opsonized red blood cells, whereas a late response (LR) was defined from the last platelet count obtained prior to another therapeutic intervention.

RESULTS

Thirty-four patients were prospectively included in the study: 21 (62%) had an increase in the platelet count; in five cases, the increase was more than 50 x 10^9/L platelets and in 16 the increase was more than 100 x 10^9/L platelets, thus defining a CR. ER were observed in 20 patients and LR were observed in seven, whereas seven patients (20%) did not respond at all (Table 1). Nine of the 20 individuals who achieved an ER had a subsequent drop in the platelet count; however, only three had a drop below 50 x 10^9/L. Six patients who relapsed underwent a subsequent splenectomy and four achieved a sustained CR. When last censored, of the 34 patients, 24 (70%) had a platelet count above 50 x 10^9/L, whereas 18 (53%) had a platelet count above 100 x 10^9/L. The 84-month thrombocytopenia-free (over 50 x 10^9/L platelets) status of the whole group is 70% (Figure 1). The increases in the platelet counts were more evident in women than in men ($p < 0.01$), in individuals younger than 18 years ($p < 0.05$) and in patients with more than 50 x 10^9/L platelets when the treatment was started ($p < 0.01$).

Nine patients displayed abnormally low levels of free haptoglobins as an evidence of hemolysis, but the hemoglobin levels did not drop more than 0.5 gr/dL in any patient. Three patients had fever after receiving the first dose of anti-D coated autologous RBC; there were no instances of hemoglobinuria or raised creatinine levels and there were no other adverse effects of the treatment. In the 14 patients who did not have an ER, the IV treatment was followed by the intramuscular delivery of anti-RhO (D)-IgG, whereas in seven individuals, two courses of anti-D opsonized RBC were delivered, 4 weeks apart.

Table 1. Salient data of the patients treated with *ex vivo* anti-D opsonized autologous red blood cells. Data on platelet counts are before the treatment (initial), immediately after the treatment (final) and in the last censored date (last).

Patient	Sex	Age	Platelet count x 10^9/L			Time (months)	Splenectomy
			Initial	Final	Last		
1	M	2	11	3	3	1	-
2	F	3	13	8	6	2	-
3	F	51	30	180	80	3	-
4	M	4	77	90	60	2	-
5	F	71	12	184	188	12	+
6	M	55	69	151	199	3	-
7	F	25	100	263	150	24	+
8	F	45	53	12	24	2	+
9	F	8	122	180	55	1	-
10	M	8	87	206	131	5	-
11	F	31	53	150	91	2	-
12	M	58	18	12	20	2	-
13	F	41	27	167	364	4	+
14	M	70	24	57	55	1	-
15	F	29	4	5	63	7	-
16	F	38	38	225	170	8	+
17	M	44	123	122	206	48	-
18	F	6	93	186	232	1	-
19	F	49	47	88	150	14	+
20	F	38	11	11	4	8	-
21	F	51	11	35	35	1	+
22	F	48	19	51	20	36	+
23	F	13	114	88	186	24	-
24	M	18	58	58	34	1	-
25	F	8	35	30	164	21	+
26	F	6	58	43	232	5	-
27	M	11	63	99	174	6	+
28	F	2	18	16	395	72	-
29	F	58	5	53	195	40	+
30	M	52	6	13	68	26	-
31	F	10	21	149	556	84	-
32	F	18	4	58	10	3	-
33	F	61	36	57	16	42	-
34	F	69	76	150	62	24	-

DISCUSSION

Our long-term results reproduce those which we had found and published previously: Approximately one half of patients treated with this approach achieve a complete remission whereas 70% reach hemostatic platelet levels, thus being able to avoid other treatments. As far as economic aspects of this therapeutic approach are concerned, it is interesting to mention that, in the treatment of patients with refractory ATP, the usual doses of IV-IgG are 2 g/Kg[2] and of IV anti-D: 50 ug/Kg,[2] whereas 100-500 ug per patient are usually enough to accomplish a full treatment with IV anti-D opsonized red blood cells.[4-6] Accordingly, we can calculate that in our country, in a 60 Kg adult the approximate costs of these treatments are: For IV-Ig: 8 400.00 USD (*Grifols*) or 30 000.00 USD (*Sandoz*), for IV-anti-D, 3200.00 USD (*Cangene-Nabi*), and for anti-D opsonized autologous erythrocytes 170.00 USD (*Cutter*). These figures indicate that a treatment with *ex vivo* anti-D coated RBC is 50-150 times cheaper than the treatment with IV-IgG. The results obtained with this treatment so far are satisfactory and similar to those which we[5,6] and others[4] had previously published using *ex vivo* anti-D coated RBC, and to the ones of other methods to achieve Fc receptor blockade.[7] These data suggest that the use of *ex vivo* anti-D opsonized RBC may represent another, substantially cheaper method to accomplish Fc-receptor blockade

as part of the treatment of patients with chronic, refractory, ATP; further studies are needed to support these observations.

REFERENCES

1. Jones HW, Tocantis LM. The history of purpura hemorrhagica. *Ann Med Hist* 1933; 5: 349-59.
2. Tarantino MD, Goldsmith. Treatment of autoimmune thrombocytopenic purpura. *Sem Hematol* 1998; 35(Suppl. 1): 28-35.
3. Pizzuto-Chávez J, Gutiérrez-Espíndola G. Plaquetas y púrpuras trombocitopénicas. En: Ruiz-Argüelles GJ (ed.). Fundamentos de Hematología. 3a In México: Editorial Médica Panamericana; 1998, p. 377-97.
4. Ambriz R, Muñoz R, Pizzuto J, Quintanar E, Morales-Polanco M, Avilés A. Low dose autologous in vitro opsonized erythrocytes. Radioimmune method and autologous opsonized erythrocytes for refractory autoimmune thrombocytopenic purpura in adults. *Arch Intern Med* 1987; 147: 105-08.
5. Ruiz-Argüelles GJ, Apreza-Molina MG, Pérez-Romano B, Ruiz-Argüelles A. The infusion of anti-RhO-(D) opsonized erythrocytes may be useful in the treatment of patients, splenectomized or not, with chronic, refractory autoimmune thrombocytopenic purpura. A prospective study. *Am J Hematol* 1993; 43: 72-3.
6. Ruiz-Argüelles GJ, López-Martínez B, Flores-Martínez J, Ruiz-Argüelles A, Pérez-Romano B. An affordable Fc-receptor blockade method for the treatment of patients with chronic, refractory autoimmune thrombocytopenic purpura. *Haematologica* 2001; 86: 481-2.
7. Scaradavou A, Bussel JB. Clinical experience with anti-D in the treatment of idiopathic thrombocytopenic purpura. *Sem Hematol* 1998; 35(Suppl. 1): 52-7.

Correspondence and reprint request:

Guillermo J. Ruiz-Argüelles MD, FRCP (Glasg)
Director General
Centro de Hematología
y Medicina Interna de Puebla
8-B Sur No. 3710
Col. Anzures
72530 Puebla, Pue.
Phone: + (522) 243 8100
Fax: + (522) 243 8428
E-mail: gruiz1@clinicaruiz.com

Recibido el 28 de febrero del 2007.
Aceptado el 9 de octubre del 2007.