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► **To cite this version:**

Alberto Alvarez-Larrán, Julio Río-Garma, Misericòrdia Pujol, Javier Rubia, Manuel Hernández-Jodra, et al.. Newly diagnosed versus relapsed idiopathic thrombotic thrombocytopenic purpura: a comparison of presenting clinical characteristics and response to treatment. *Annals of Hematology*, 2009, 88 (10), pp.973-978. 10.1007/s00277-009-0707-9 . hal-00535035

HAL Id: hal-00535035

<https://hal.science/hal-00535035>

Submitted on 11 Nov 2010

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Newly diagnosed versus relapsed idiopathic thrombotic thrombocytopenic purpura: a comparison of presenting clinical characteristics and response to treatment

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Received: 28 September 2008 / Accepted: 26 January 2009 / Published online: 11 February 2009
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Abstract The remission rate with plasma exchange (PE) in thrombotic thrombocytopenic purpura (TTP) exceeds 80%, but the disease relapses in up to 20–30% of the cases. Clinical characteristics and response to treatment of relapsed TTP are not well defined. The objective of the present study was to compare the clinical and biological characteristics at presentation and the response to treatment between de novo and relapsed TTP. For such purpose, a total of 102 episodes of idiopathic TTP (70 de novo and 32 relapses) included in a recent

multicentric prospective cohort study were analysed. All patients were homogeneously treated with daily PE and corticosteroids. In comparison with de novo TTP, episodes of relapsed TTP showed a higher Hb level (median, 122 g/l versus 91 g/l, $p < 0.001$) and lower serum lactate dehydrogenase (2.2- versus 4.5-fold above the upper limit of normality, $p < 0.001$). Neurological symptoms and fever were less frequently observed in patients with relapsed TTP than in patients with de novo TTP. Patients with relapsed TTP needed fewer PE sessions

Alberto Alvarez-Larrán and Julio del Río-Garma contributed equally to this article.

Grant support: This work was supported in part by a grant awarded by the Ministry of Health of the Government of Spain (FIS 05/2189).

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(five versus ten, $p = 0.02$) and a smaller volume of plasma (221 ml/kg versus 468 ml/kg, $p = 0.004$) to achieve remission than those with de novo TTP. There was no significant difference in the rate of recrudescence under treatment, the need of complementary treatments or the frequency of refractoriness to PE therapy. In conclusion, relapsed TTP has a milder clinical profile and responds more easily to PE than de novo TTP.

Keywords Thrombotic thrombocytopenic purpura · ADAMTS13 · Plasma exchange · Relapse

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare haematological disorder characterised by microangiopathic haemolytic anaemia, consumptive thrombocytopenia, neurologic involvement and the formation of platelet-rich thrombi into the small vessels [14]. Many patients with idiopathic TTP have a deficient ADAMTS13 activity, mostly as a consequence of inhibitory autoantibodies, with this leading to widespread von Willebrand factor-mediated platelet aggregation [2]. Plasma exchange (PE) with massive plasma infusion produces disease remission in more than 80% of patients, presumably because it replaces the defective ADAMTS13 and/or removes the causative antibody [15, 16]. Nevertheless, 20–50% of patients who attain disease remission experience one or more relapses, usually within the 2 years that follow the initial episode [18, 19]. Some recent data point to an increased risk of relapse in patients with persistently inhibitory antibodies and/or severe ADAMTS13 deficiency after clinical remission [6, 13].

Although it is a common belief that relapses of TTP present with less severe clinical manifestations [7, 8, 11], there are few studies on which to support such a conviction.

Indeed, the published experience on the presentation and prognosis of relapsed TTP is scarce and consists mainly of retrospective studies, case reports and small series whose analysis was rather focused on the response to complementary treatments such as splenectomy or rituximab [1, 10, 24]. Moreover, differences between authors in the definition of relapse and the inclusion of patients with haemolytic uremic syndrome or secondary TTP in some studies further compound drawing the specific features of relapsed as compared with de novo idiopathic TTP [7, 8, 20, 21, 23].

We have recently assessed the therapeutic efficacy of different kinds of plasma in a prospective cohort of idiopathic TTP patients in which nearly one third of the acute episodes were relapses of a previously known TTP [4]. We herein report on the clinical and biological characteristics at presentation, as well as on the response to treatment of relapsed TTP as compared with de novo TTP.

Materials and methods

Patients and study design

All patients with idiopathic TTP consecutively seen at 31 hospitals in Spain from October 2004 to October 2007 were treated by PE according to a homogeneous protocol and included in a multicentric, prospective cohort study. Although some patients had presented the first or subsequent episodes of TTP before October 2004, these episodes preceding the study starting date were not analysed. Informed consent for the scientific use of the patients' clinicohematological data and biological samples was obtained at diagnosis according to each centre's ethical committee. Details on the patient inclusion criteria and the treatment protocol have been published elsewhere [4]. In brief, the diagnosis of idiopathic TTP was based on the presence of haemolytic anaemia with schistocytes in the blood smear and thrombocytopenia in the absence of renal failure, a positive antiglobulin test, disseminated intravascular coagulation, malignant hypertension, neoplasm, stem cell transplantation, concurrent infection or positive HIV serology. Disease severity at presentation was evaluated by Rose and Eldor score [17]. The patient's first medical attendance was established as the TTP debut. ADAMTS13 activity and inhibitory autoantibodies were assessed by the collagen-binding affinity method [9]. The treatment schedule consisted of daily PE with replacement of more than 30 ml of plasma per kilogram of body weight and prednisone (1.5 mg/kg/day) until the platelet count was above $150 \times 10^9/l$ for three consecutive days, at which time the frequency of PE was reduced to several times per week before being stopped. All the patients were treated according to this schedule for the first 7 days. Thereafter, if the

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patient had not attained a response, the attending physicians were free to use any adjuvant treatment at their discretion.

Response to treatment was defined as a platelet count of $>150 \times 10^9/l$ for more than three consecutive days, normal serum lactate dehydrogenase (LDH) activity and absence of any TTP-related sign or symptom. Recrudescence was defined as a decrease in platelet count below $50 \times 10^9/l$ (or below 50% of the highest platelet count previously achieved) while on PE treatment. Responses that eventually lasted for longer than 30 days after withdrawal of PE therapy were considered as remissions. Relapse was defined as disease reappearance after a remission had been achieved.

The relationship between the type of TTP episode (de novo versus relapse) and the patient characteristics and outcomes was analysed by the chi-square test for binary variables or the Mann–Whitney rank test for continuous or ordered data. Since the response to PE is influenced by the kind of plasma used as replacement fluid [4], the association between type of TTP episode (de novo or relapse) and remission status by the eighth day was analysed by logistic regression conditional on the kind of plasma. That analysis allows the effect of the type of episode to be adjusted by other prognostic variables within each group of plasma used for fluid replacement. The prognostic variables included in the regression model were the type of TTP episode (de novo versus relapse), the Rose

and Eldor score (<5 versus ≥ 5), the volume of plasma replaced in the first 7 days (<280 ml/kg versus ≥ 280 ml/kg) and the time lapsed between the debut of the TTP episode and the start of PE (<5 days versus ≥ 5 days). Calculations were carried out using the software SPSS 12.0.

Results

Patient characteristics

One hundred and two TTP episodes were analysed. Seventy-eight patients contributed with one episode during the study period (62 de novo and 16 relapses), and 12 patients contributed with two episodes each (eight de novo and 16 relapses). In total, 70 out of the 102 episodes were a newly diagnosed TTP, whereas 32 were relapses of a previously known TTP. Relapses corresponded to a second TTP episode in 15 cases, a third episode in seven cases, a fourth episode in four cases and a fifth episode in six cases. The median time elapsed from the previous episode to relapse was 16 months (range 1.1–110). This interval of time was shorter for second episodes than for third or higher order episodes [median (range), 9 (1.1–70) months and 24 (5–110) months, respectively, $p = 0.001$].

Table 1 summarises the main clinical and laboratory data at presentation of the 102 TTP episodes according to the

Table 1 Clinical and laboratory features at presentation in 102 episodes of idiopathic thrombotic thrombocytopenic purpura according to the type of episode

Variable	De novo $N=70$	Relapsed $N=32$	p
Age, years	40 (18–77)	37 (19–79)	ns
Female gender, n (%)	51 (73)	23 (72)	ns
Fever, n (%)	17 (24)	1 (3)	0.01
Weakness, n (%)	59 (84%)	8 (25%)	<0.001
Bleeding, n (%)	46 (66%)	21 (66%)	ns
CNS involvement, n (%)	44 (63)	8 (25)	0.001
Hb, g/dl	8.1 (4.4–12.4)	12.2 (6.6–16.2)	<0.001
≥ 10 g/dl, n (%)	13 (19)	27 (84)	<0.001
<10 g/dl, n (%)	57 (81)	5 (16)	
Platelets $\times 10^9/l$	13 (2–61)	19 (7–79)	0.02
$\geq 20 \times 10^9/l$, n (%)	19 (27)	16 (50)	0.04
$<20 \times 10^9/l$, n (%)	51 (73)	16 (50)	
Serum creatinine, mg/dl	1 (0.3–2.6)	0.9 (0.5–2.1)	0.08
Serum LDH ^a	4.5 (1.3–15.4)	2.2 (1.1–7.5)	0.002
Severity score ^b	4.5 (1–7)	2 (1–6)	<0.001
≥ 5 , n (%)	35 (50)	2 (6)	<0.001
<5 , n (%)	35 (50)	30 (94)	
ADAMTS13 $<5\%$, n (%) ^c	28 (72%)	13 (81%)	ns
ADAMTS13 inhibitor, n (%) ^c	34 (87%)	13 (81%)	ns
Days until treatment	1 (0–34)	1 (0–3)	ns
≥ 5 days, n (%)	9 (13)	0 (0)	0.05
<5 days, n (%)	61 (87)	30 (100)	

Continuous variables are expressed as median (range)
CNS central nervous system, ns not significant at the 0.05 level

^a LDH observed in the patient/upper limit of normality of the corresponding laboratory

^b According to the score by Rose and Eldor [17]

^c Out of 55 assessable patients

type of episode (de novo or relapse). Both groups of patients were comparable with regard to age and gender, and there was no statistically significant difference in the percentage of patients with a severe deficit of ADAMTS13 activity or with inhibitory autoantibodies. Patients with relapsed TTP presented less frequently with fever, weakness or neurological involvement and had on average higher haemoglobin levels, lower serum LDH activity and lower severity scores.

In 15 (47%) out of the 32 relapse episodes, the only clinical finding was mild mucocutaneous bleeding. Two patients presented with weakness as the single manifestation of relapse. In two additional patients, the relapse was diagnosed after the unexpected finding of thrombocytopenia in routine laboratory evaluations performed 1.2 and 12 months, respectively, after the preceding TTP episode. In contrast, only six (9%) out of the 70 patients with de novo TTP presented with mucocutaneous bleeding as the only clinical manifestation.

In the vast majority of the relapse episodes, no precipitating factor was found. In two cases, the relapse was associated with concomitant infection and in one case with pregnancy. Early institution of PE was the norm in relapsed TTP since it was started within 3 days from disease's debut in every case, whereas in nine of the 70 de novo episodes, PE was delayed for five or more days ($p = 0.05$, Table 1).

Treatment intensity and complementary therapy

Intensity of initial treatment, as measured by the total volume of plasma infused in the first 3 and 7 days of treatment, was similar in both groups (Table 2). After the eighth day of treatment and because of delayed response to PE, adjunctive therapy was added to the therapeutic schedule in 30 patients. Vincristine was administered in 20 patients (17 de novo TTP and three relapsed TTP). In the relapse group, one patient received vincristine after 11 PE sessions, and two additional patients received vincristine “out of protocol” on days 1 and 4, respectively. Rituximab was administered in six de novo and three relapse episodes, in the latter after ten, 13 and 36 PE sessions. Four patients underwent splenectomy due to lack

of response to PE (three patients with de novo TTP and one patient in the relapse group after 14 PE procedures). Some patients received more than one modality of complementary therapy. Six additional patients in the relapse group received rituximab in remission, after the last PE procedure, as prophylaxis of new relapses. Differences between both groups in the number of patients receiving vincristine or rituximab or submitted to splenectomy did not attain statistical significance.

Treatment outcomes

Overall, remission was eventually achieved in 66 (94%) de novo episodes and all the relapse episodes. Four out of 70 patients with de novo TTP did not attain a remission and died from progressive TTP after eight, 11, 20 and 22 PE sessions, respectively. Patients with relapsed TTP required on average less PE sessions and a smaller volume of plasma to achieve remission (Table 2). As shown in Table 2, remission by day 8 since the start of plasma exchange was more frequently achieved in relapses than in newly diagnosed TTP (69% versus 41%, $p = 0.02$). After statistical adjustment for other potential prognostic factors and taking into account the effect of the kind of plasma used for fluid exchange, the likelihood of being in remission by the eighth day of treatment was higher in relapses than in de novo TTP [OR 6.8, 95% CI 2–23; $p = 0.002$]. All relapsed patients who received complementary treatment required a variable number of additional PE procedures to achieve remission (one, four and five PE sessions, respectively, in those receiving vincristine; one, two and 15 PE procedures in those receiving rituximab; and 24 PE sessions in the patient submitted to splenectomy).

Discussion

The present study compares the clinical and laboratory features, as well as the response to PE between 70 acute episodes of de novo idiopathic TTP and 32 relapse episodes that were all diagnosed and treated according to a homogeneous protocol. To the best of our knowledge, this

Table 2 Intensity of initial treatment and response to plasma exchange therapy in 102 episodes of idiopathic thrombotic thrombocytopenic purpura according to the type of episode

Continuous variables expressed as median (range)
 ns not significant at the 0.05 level

Variable	De novo $N=70$	Relapsed $N=32$	p
Plasma infused in the first 3 days, ml/kg	140 (90–239)	122 (100–183)	ns
Plasma infused in the first 7 days, ml/kg	313 (211–507)	280 (209–408)	ns
Remission on day 8, n (%)	29 (41)	22 (69)	0.02
Recrudescence, n (%)	28 (40)	9 (28)	ns
Mortality, n (%)	4 (6)	0 (0)	ns
No. of PE to remission	10 (2–52)	5 (2–38)	0.004
Plasma infused to remission, ml/kg	468 (75–3108)	221 (95–1539)	0.001

is the biggest series reporting on the relapse of idiopathic TTP. Our results show that relapsed TTP usually presents with mild clinical manifestations, often consisting of isolate thrombocytopenia with or without mucocutaneous bleeding; CNS involvement is less frequent and less severe than in de novo TTP, and many patients present with normal haemoglobin levels or only moderate anaemia.

In our patients with relapsed TTP, the time elapsed between the disease onset and the initiation of PE was shorter than in de novo TTP, probably because patients were aware of the clinical manifestation of TTP and instructed to quickly seek medical attention at the first sign of relapse and also because the attending physicians were cognisant of the patient's previous diagnosis. It is worth noting that bruising due to thrombocytopenia was by large the most common early sign of relapse and that isolate, asymptomatic thrombocytopenia found at a regular follow-up control was the first sign of relapse in two additional patients. The lower serum LDH levels found in relapses as compared with de novo TTP is another hint of milder disease. The high serum LDH levels that are distinctive of acute, newly diagnosed TTP reflect the extent of tissue ischemia caused by platelet thrombi into the small vessels more than the degree of haemolysis [3] so that the moderate LDH increases found in relapses would point to a less widespread microvascular involvement.

Response to PE was faster in relapses than in newly diagnosed TTP as demonstrated by a lower number of PE sessions and a smaller volume of plasma to achieve remission. Furthermore, disease remission was eventually achieved in all relapse episodes, whereas four out of 70 patients with de novo TTP died from unresponsive disease. The excellent response rate of relapsed TTP probably relates to the milder clinical presentation and the shorter delay in initiating PE. Long delays in making the diagnosis of TTP and initiating PE have been associated with progression of CNS involvement and treatment failure [5, 12].

Alternatively, the good prognosis of relapsed TTP might rely on differences in the pathophysiology of TTP between patients who relapse and patients who do not. Recent reports have pointed out that persistence of severe ADAMTS13 deficiency, and inhibitory antibodies during clinical remission would increase the likelihood of TTP relapse [6, 13], and previous studies suggested a better response to PE in patients with severely deficient ADAMTS13 as compared to those with less severe deficit [22, 25]. Our study does not allow drawing any conclusion about the predictive value of ADAMTS13 levels or inhibitory antibodies since they were not measured during clinical remissions. However, the frequency of both laboratory features, measured at the beginning of the acute episode, did not significantly differ between patients with

de novo or relapsed TTP. On the other hand, the better response rate seen in relapse patients cannot be ascribed to a more intensive treatment since both groups of patients were exchanged, on average, with similar volumes of plasma during the first days of treatment.

In summary, the present study shows that relapsed TTP usually presents with milder clinical and laboratory features than de novo TTP, mostly isolated thrombocytopenia and bruising, and responds quickly and predictably to PE with plasma infusion.

Acknowledgements

Contribution A.A.-L, J.D.R.-G and A.P. designed the study, managed the data, performed the statistical analysis and draft the article; M.P, J.D.R and M.H.J. designed the study, managed the clinical data, revised and approved the final version of the article; J.R.G, J.M.G.G, A.V, L.E, C.A, J.A.G.E and A.G.N managed the clinical data, revised and approved the final version of the article. M.B. performed the ADAMTS13 assays.

Conflict of interest disclosure The authors declare no competing financial interests.

Study group members The following investigators participated in the Spanish Apheresis Study Group (GEA): M.D. Castellá, Hospital Vall d'Hebron, Barcelona; F. Moscardó, Hospital La Fe, Valencia; M. Corral, Hospital Clínico Universitario, Salamanca; P. Rodríguez-Vicente, Hospital Central de Asturias, Oviedo; L. Enríquez, Hospital do Meixoeiro, Vigo; C. Ramírez y R. González, Hospital Juan Canalejo, A Coruña; M.A. Canales, Hospital La Paz, Madrid; C. Zamora, Hospital Ramón y Cajal, Madrid; E. Contreras, Hospital Joan XXIII, Tarragona; J. Muncunill, Hospital Son Dureta, Palma de Mallorca; A. Alegre, Hospital de la Princesa, Madrid; E. Gómez-Arteta, Hospital San Pedro de Alcántara, Cáceres; I. Teruel, Hospital Clínico Universitario, Valencia; A. Vidaller and J. Muñoz, Hospital de Bellvitge, Hospitalet de Llobregat; A. Insunza and I. Romón, Hospital Marqués de Valdecilla, Santander; M.J. Muñoz, Hospital de Móstoles, Madrid; C. Paniagua, Fundación Jiménez Díaz, Madrid; D. Gutierrez and A. Rodríguez, Hospital Virgen de la Macarena, Sevilla; J.R. Grifols and A. Serrano, Hospital Germans Trias i Pujol, Badalona; A. Campos and M. Villamayor, Hospital Clínico Universitario, Santiago de Compostela; A. de Andrés, Hospital Xeral Calde, Lugo; J.M. Jiménez, Hospital Virgen del Rocío, Sevilla; J. Plaza, Hospital Xeral-Cies, Vigo; A. García-Coca, Hospital Clínico Universitario, Valladolid; M. Casanueva, Hospital 12 de Octubre, Madrid; M.J. Uriz and M.L. Antelo, Hospital de Navarra, Pamplona; E. Carreter, Hospital General, Lanzarote; A. Peña and L. Llorente, Hospital Clínico San Carlos, Madrid; A. Gómez-Pineda and J. Anguita, Hospital Gregorio Marañón, Madrid; R. López and J.A. Muñoz, Hospital Virgen del Mar, Cádiz.

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