

## TREATMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA WITH HIGH-DOSE IMMUNOGLOBULINS. RESULTS IN 17 PATIENTS

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### ABSTRACT

**Background.** The experimental observation that plasma from TTP patients sometimes exhibits a protein which can cause platelet agglutination, and that such agglutination can be inhibited in vitro by the use of IgG led some authors to treat plasma exchange-resistant TTP patients with high-dose IgG (HDIGG).

**Methods.** We report the results obtained with HDIGG treatment in 17 patients retrospectively examined by the Italian Cooperative Group for the study of TTP: 6 males and 11 females, mean age was 31.7 years for the women (range: 20-65) and 44.6 for the men (range: 26-66). In all cases HDIGG administration was combined with other treatment modalities.

**Results.** Of the 17 patients, 7 died from disease progression (41.1%), 2 achieved partial remission (11.7%) and the remaining 8 achieved complete remission (47%). Of the 10 cases (58.8%) with a positive response, only in 4 did the addition of HDIGG seem to produce significant improvement. All efforts made to characterize the subgroup of patients who responded to HDIGG and compare them with the non responders failed.

**Conclusions.** Although our results do not unquestionably demonstrate the role of HDIGG in the treatment of TTP, they suggest a possible role for HDIGG in the treatment of those rare plasma exchange-resistant TTP cases.

*Key words:* thrombotic thrombocytopenic purpura, high-dose immunoglobulins, salvage treatment

Thrombotic thrombocytopenic purpura (TTP) is an uncommon syndrome characterized by thrombocytopenia, microangiopathic anemia, fever, signs of neurologic and/or renal involvement.<sup>1</sup> Its etiology is unknown and its prognosis, which was very unfavorable in most patients up to the late '70s, has markedly improved thanks to plasma exchange techniques, so that 70-90% of patients can now be cured.<sup>2-5</sup>

However, since some patients either do not respond or relapse after remission, complemen-

tary or alternative therapies to plasma exchange such as cortisone,<sup>6</sup> antiplatelet agents,<sup>7</sup> splenectomy,<sup>8</sup> vincristine,<sup>9</sup> cyclophosphamide,<sup>10</sup> prostacyclin<sup>11</sup> and plasmapheresis with plasma cryosupernatant<sup>12</sup> have been proposed at some time.

In this paper, we report the results obtained with high-dose IgG (HDIGG) treatment in 17 patients retrospectively examined by the Italian Cooperative Group for the study of TTP (see *Appendix*). The rationale for using HDIGG in TTP patients is based on relatively few, but interesting data – i.e. the experimental observa-

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tion that HDIgG inhibit platelet aggregation induced by plasma from TTP patients,<sup>13</sup> and the positive results obtained in the treatment of idiopathic thrombocytopenic purpura (ITP).<sup>14-16</sup> In ITP, whose etiology is definitely autoimmune, IgG are reported to follow two main patterns: first, early competitive inhibition of the bond between circulating antibodies and platelets, and between antibodies adhering to platelets and Fc macrophage receptors, and second, the probable long-term stimulation of the T system with consequent partial suppression of antibody production.<sup>14</sup> Thus, a possible autoimmune etiology of TTP, which had been proposed in the past,<sup>17</sup> represents another reason to test HDIgG in this disease.

### Materials and Methods

Seventeen patients affected by TTP were treated with HDIgG from January 1987 through June 1993 in several Italian hospitals.

TTP was diagnosed on the basis of the following signs: thrombocytopenia ( $<100 \times 10^9/L$ ), microangiopathic anemia (demonstrated by the presence of schizocytes in peripheral blood smears), no disseminated intravascular coagulation, no anti-erythrocyte or anti-platelet antibodies, high LDH levels, signs of neurological and renal involvement (Table 1). A diagnosis of hemolytic-uremic syndrome (HUS) was ruled out since all patients showed only slight signs of renal involvement; as a matter of fact, none of our patients displayed serum BUN or creatinine values exceeding 60 mg% or 1.3 mg%, respectively. The only signs of kidney damage were the presence of microhematuria and/or cylindruria at urinalysis.

Six of the 17 patients were males and 11 were females; mean age was 31.7 years for the women (range: 20-65) and 44.6 for the men (range: 26-66).

Two women were positive for anti-nDNA antibodies; in one of them systemic lupus erythematosus (SLE) had already been diagnosed according to ARA criteria but was clinically in remission at TTP onset, while antinuclear antibodies were an occasional finding in the other patient, in the absence of any other diagnostic

Table 1. Clinical features and laboratory findings in 17 TTP patients treated with HDIgG. Regarding the signs of renal impairment, a diagnosis of HUS was ruled out since all patients showed only microhematuria and/or cylindruria at urinalysis.

#	Age	Sex	Hb (g/dL)	Plt ( $\times 10^9/L$ )	LDH (mU/mL)	Signs of neurological impairment	Signs of renal impairment	Fever
1	26	F	6.6	8	2370	Yes	Yes	Yes
2	58	M	9.0	41	1123	Yes	Yes	Yes
3	52	F	9.1	29	834	Yes	Yes	Yes
4	26	F	8.6	10	2365	No	Yes	Yes
5	26	F	6.4	10	2244	Yes	Yes	Yes
6	21	F	7.4	19	4522	Yes	Yes	No
7	26	M	5.1	9	2047	Yes	Yes	Yes
8	53	F	11.8	10	3780	Yes	No	No
9	36	M	7.2	11	2761	Yes	Yes	No
10	52	M	8.9	19	963	Yes	Yes	No
11	29	M	7.6	18	939	Yes	Yes	No
12	45	F	6.4	20	173	Yes	No	No
13	22	F	7.9	40	438	Yes	No	No
14	26	F	5.9	20	1700	Yes	No	Yes
15	66	M	7.4	23	3611	Yes	Yes	No
16	60	F	6.9	8	8231	Yes	Yes	No
17	20	F	6.8	19	2657	Yes	No	No

criterion for SLE.

In one woman TTP was the onset sign of an occult tumor, while another patient had lung cancer, which had been treated with mitomycin-C up to six months before this study and was recurring.

All patients received IgG doses of 400 mg/kg/day in 1-20 infusions. HDIgG was always combined with other treatment modalities – i.e. with cortisone in all cases, plasma exchange in 15, platelet anti-aggregating drugs in 11, heparin in 2, and lastly plasma infusion in 2 cases (Table 2).

Criteria for evaluation of response to treatment, both complete and partial, were those agreed upon by members of the Italian Cooperative Group for TTP (Table 3).

### Results

Of the 17 patients treated with HDIgG and other treatment modalities, 7 died of disease progression (41.4%), 2 achieved partial remission (11.7%), and the remaining 8 achieved

Table 2. Therapy before HDIgG administration and outcome.

#	Plasma exchange	Plasma infusion	Anti-platelet drugs	Cortisone	Heparin	Outcome
1	+		+	+	+	Died
2	+		+	+		CR
3	+			+		CR*
4	+			+		CR
5	+			+		Died
6	+		+	+		CR**
7	+			+		PR
8		+	+	+		CR*
9	+		+	+		CR**
10	+		+	+		Died
11	+		+	+		PR
12	+			+		Died
13		+	+	+		Died
14	+		+	+		CR**
15	+		+	+		Died
16	+			+	+	Died
17	+		+	+		CR**

\*PE and HDIgG were administered together from the onset; \*\* patients who did not respond to HDIgG administration but responded to other treatments; \*\*\* HDIgG responders.

complete remission (47%).

Of the 8 patients who achieved complete remission, only in 4 did the addition of HDIgG to the earlier treatment produce significant improvement.

In all 4 of these cases the former therapy, which consisted of repeated cycles of plasma exchange (11, 11, 24 and 11, respectively) combined with cortisone and platelet anti-aggregating substances – i.e. aspirin in 2 cases, aspirin plus dipyridamole in another case and ticlopidine in the last one – had yielded no results in 3 cases, while the fourth patient experienced a brief complete response immediately followed by a quick relapse.

QM, a woman, after an early increase in platelet count and reduction in LDH levels, quickly worsened although she was receiving plasma exchange, platelet anti-aggregating substances (aspirin and dipyridamole) and cortisone. HDIgG were then combined with the former treatment and complete remission was achieved after 21 plasma exchange sessions and 14 days of HDIgG (Figure 1a).

RR, a man, in spite of plasma exchange, corti-

Table 3. Criteria for evaluation of response to treatment in TTP patients.

Complete remission:	platelets > 150×10 <sup>9</sup> /L reticulocytes < 100×10 <sup>9</sup> /L LDH < 300 U/L azotemia < 50 mg% creatinine < 1.2 mg% haptoglobin > 40 mg%
Partial remission:	platelets < 100×10 <sup>9</sup> /L LDH < 300 U/L

sone and ticlopidine showed recurrent advanced seizures to stage-III coma during plasma exchange session #3. Seven plasma exchange sessions followed without results. Thus, HDIgG infusion was added to the former treatment. Laboratory data improved, and five days later the patient woke from the coma. Complete clinical and hematologic remission was achieved after 27 plasma exchanges and 20 immunoglobulin administrations (Figure 1b).

CL, a woman, after early response to plasma exchange (12 sessions) and aspirin, relapsed when treatment was interrupted. Remission was achieved again after 12 more cycles of plasma exchange, but the patient relapsed again 8 days after interrupting treatment. HDIgG were then administered and complete and long-lasting remission was finally achieved (Figure 1c).<sup>18</sup>

VB, a woman, failed to respond to combined acetylsalicylic acid and plasma exchange, while her neurologic status worsened. Therefore HDIgG were administered. From the second day of treatment a gradual normalization was observed in the patient's hematochemical variables, and at day 5 complete remission was attained, with complete resolution of neurologic symptoms (Figure 1d).<sup>19</sup>

In the other 4 patients who achieved a complete remission, HDIgG infusion was ineffective and a positive response was obtained in other ways, i.e. by means of continuous plasma exchange, vincristine boluses, and combined ticlopidine (2 patients).

In the two patients who achieved only a partial remission, HDIgG were administered from the beginning in combination with plasma exchange and other treatment modalities (cor-

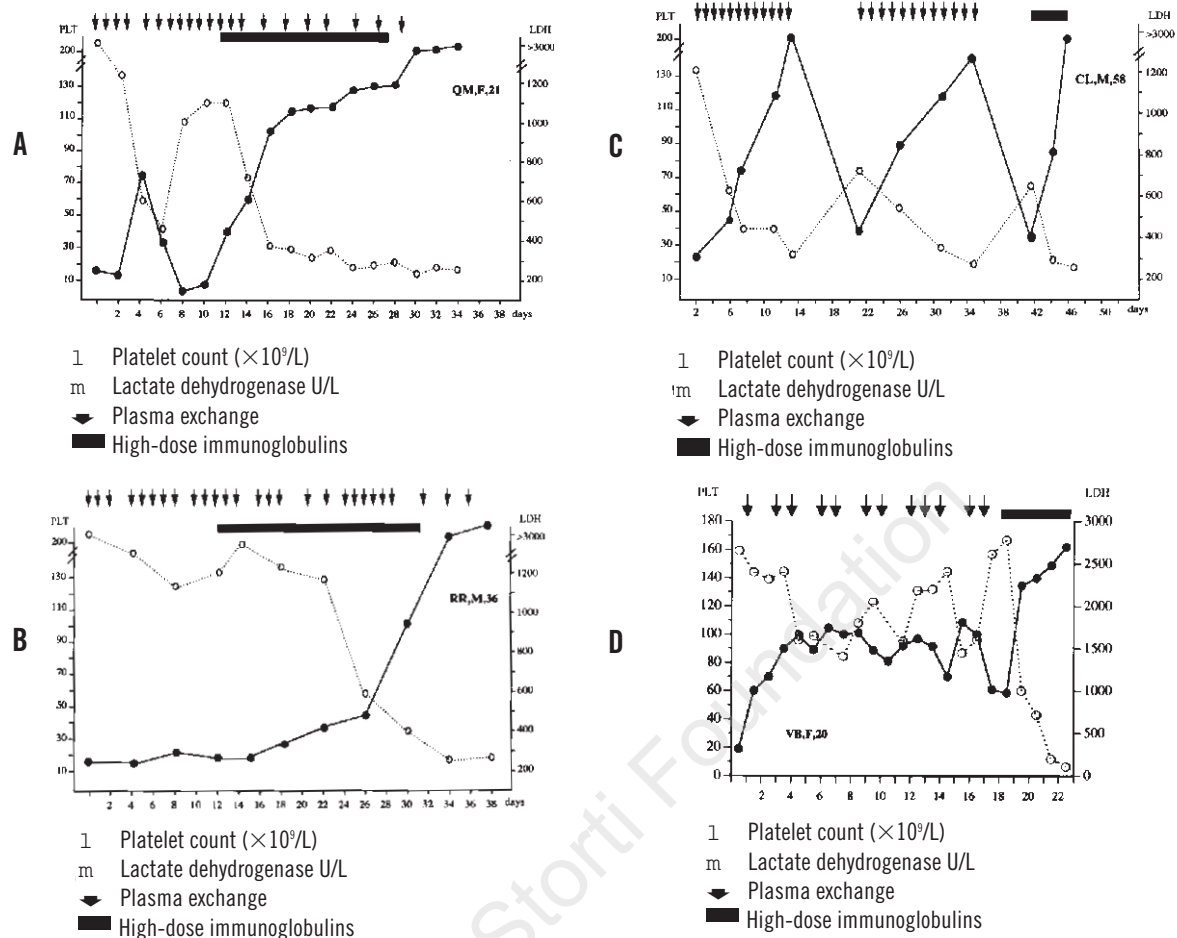


Figure 1, a,b,c,d. Changes in platelet count and LDH levels during HDIgG treatment in the four TTP cases who achieved CR with HDIgG infusion.

tisone and cortisone together with aspirin, respectively), so that the role of each individual agent in achieving this response is difficult to assess. Moreover, complete remission was obtained by restarting the exchange treatment without HDIgG.

Thus, excluding these 2 patients, complete remission with the aid of HDIgG infusion was obtained in 4/15 cases (26.6%).

### Discussion

Plasmapheresis combined with plasma infusion is the only therapy considered to be effective and irreplaceable for the treatment of TTP, which suggests the value of removing a possible cause as well as administering a possibly lacking factor.<sup>2,20</sup>

Several observations support the presence of one or more factors causing platelet aggregation, the nature of which may be that of a small protein,<sup>21</sup> a cysteine-proteinase<sup>22</sup> or large von Willebrand factor (vWF) multimeric forms.<sup>23</sup>

In all these cases, plasma exchange allows the involved factor to be removed while the replacement of drawn plasma with fresh frozen plasma from a donor helps restore normal plasma inhibitory action.<sup>24</sup> Moreover, plasma exchange can stimulate the production of prostacyclin,<sup>25</sup> protract its activity,<sup>26</sup> or help the conversion of large vWF multimers into smaller forms.<sup>27</sup>

The infusion of fresh frozen plasma alone is sometimes effective, but in most cases it fails.<sup>4,28,29</sup>

Platelet aggregation induced by plasma from TTP patients can be inhibited by means of nor-

Table 4. Inadequacy of both Rose and Eldor's severity score (based on four clinical and laboratory parameters: neurologic findings, renal function impairment, platelet count, and hemoglobin value at presentation) and Dones' pure neurologic score to differentiate between HDIgG responders and non responders.

	Patients who achieved a CR with HDIgG (n = 4)	Patients who died despite HDIgG treatment (n = 7)	Difference
Average Severity Score (Rose and Eldor, 1987) <sup>37</sup>	6.0	5.57	n.s.
Average Neurologic score (Dones, 1992) <sup>5</sup>	2.75	2.57	n.s.

mal plasma or immunoglobulins G,<sup>13</sup> hence the attempts to cure the disease with HDIgG. Most of the results reported in the literature are usually positive,<sup>18,19,30-33</sup> even though some disagree.<sup>34</sup> In fact, the actual role of IgG is difficult to assess for it is not easy to say when a patient should be considered unresponsive to earlier treatment modalities.

In a series of 7 TTP episodes, the combination of plasma exchange and HDIgG produced a remission in 85% of cases;<sup>35</sup> however, this figure is similar to that obtained by other authors with plasmapheresis alone.<sup>20</sup>

In one case HDIgG were combined with prednisone, which had been administered for 10 days without improvement, and remission was quickly achieved.<sup>30</sup> On the other hand, in a large series as many as 28% of TTP patients responded to prednisone alone.<sup>4</sup>

More recently, Finazzi *et al.* in a prospective, non-randomized study compared the efficacy of intravenous immunoglobulins with plasma exchange in 17 consecutive adult patients with TTP/HUS.<sup>36</sup> The results of this study confirmed plasma exchange as the treatment of choice in this disease, since no responses were observed in the 3 patients treated with immunoglobulins (versus 10/14 responses in the plasma exchange arm).<sup>36</sup> Our results do not be unequivocally demonstrate the role of HDIgG in the treatment of TTP.

As a matter of fact, HDIgG failed in 7 cases who had not responded to more conventional treatments earlier.

A partial remission was achieved in 2 patients, but the exact role of HDIgG in these cases is hard to assess, since this treatment was associated from the beginning with other therapeutic modalities; furthermore, complete and

lasting remission was achieved without HDIgG.

In the other 8 patients, HDIgG seem to have provided a formerly unobtainable positive response in 4 patients only, while in the remaining 4 cases HDIgG proved to be ineffective and patients were saved other treatment modalities.

The high mortality rate (41.1%) observed in our series is probably accounted for by the high percentage of patients who did not respond to plasma exchange. Moreover, disease was secondary to SLE (2 cases) and to active cancer (2 cases); the presence of such primary conditions might have affected TTP evolution.

Since only 4 patients were cured with HDIgG, we made an effort to characterize this subgroup in terms of prognostic factors and to compare them with those patients who did not respond and ultimately died from the disease.

Unfortunately, no useful indications emerged from this analysis. Indeed, neither the severity score proposed by Eldor and Rose in 1987,<sup>37</sup> nor the neurological score elaborated by Dones in 1992, which proved to be useful for prognostically characterizing 84 TTP patients retrospectively analyzed by the Italian Cooperative Group for TTP,<sup>5</sup> allowed us to identify any relevant prognostic factors (Table 4).

It is likely that, due to the heterogeneous nature of TTP and its possibly multiple etiopathogenesis, HDIgG play a role in selected cases only, which cannot be identified a priori. Therefore, in our opinion, HDIgG should only be used like other alternative treatment modalities such as immunosuppressants and splenectomy in those patients who do not respond to conventional plasma exchange.

So far, not enough data are available to consider HDIgG the treatment of choice, either alone or in combination with other modalities,

for TTP patients. As previously suggested,<sup>36</sup> further information should be collected by well-designed clinical trials rather than from additional single case reports.

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**Appendix**

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