ANTIPLATELET AGENTS IN THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP). RESULTS OF A RANDOMIZED MULTICENTER TRIAL BY THE ITALIAN COOPERATIVE GROUP FOR TTP

Enrico Bobbio-Pallavicini,* Luigi Gugliotta,° Riccardo Centurioni,# Camillo Porta,@ Nicola Vianelli,° Atto Billio,^ Fiorenzo Tacconi,* Edoardo Ascari§ for the Italian Cooperative Group for TTP (see Appendix)

Divisione di Medicina Generale, Ospedale Maggiore di Crema, Crema; °Istituto di Ematologia "L. & A. Seràgnoli", Università degli Studi di Bologna, Policlinico Sant'Orsola, Bologna; #Istituto di Clinica Medica, Università degli Studi di Ancona, Policlinico di Torrette, Ancona; @Dipartimento di Medicina Interna e Nefrologia, Università degli Studi di Pavia, I.R.C.C.S. Policlinico San Matteo, Pavia; ^Divisione di Ematologia, Ospedale Generale di Bolzano, Bolzano; §Istituto di Medicina Interna e Oncologia, Università degli Studi di Pavia, I.R.C.C.S. Policlinico San Matteo, Pavia, Italy

ABSTRACT

Background and objective. Antiplatelet agents are often included in plasma exchange-based regimens for thrombotic thrombocytopenic purpura (TTP) patients; however, the opportuneness of their use in TTP is still controversial. The Italian Cooperative Group for TTP carried out a randomized trial to investigate their actual effectiveness, both in acute TTP and as maintenance treatment.

Methods. Seventy-two TTP patients were randomized to receive plasma exchange and steroids with (group B) or without (group A) aspirin and dipyridamole. Treatment efficacy was evaluated after 15 days and salvage treatments were also considered for non-responders. Upon disease remission, the patients already treated with antiplatelet agents received ticlopidine for one year.

Results. Regarding the treatment of acute phase TTP, similar overall response rates were observed in the two groups (91.4% in group B vs. 75.6% in group A), but lower mortality rates were observed at 15 days in the patients treated with antiplatelet agents; as a matter of fact, 5 patients from arm A died in the first 15 days (13.5%) versus only one in arm B (2.8%). These figures, while not statistically significant, seem to suggest that antiplatelet agents might be useful in preventing deaths in acute TTP; moreover, bleeding did not worsen in antiplatelet agent-treated patients. As for the role of maintenance treatment, our results support the efficacy and safety of one-year ticlopidine therapy since the current relapse rate is significantly higher in non-treated patients; as a matter of fact, 6 patients (21.4%) in the non-ticlopidine group and only 2 (6.25%) in the ticlopidine group relapsed (p = .0182 in favor of maintenance treatment).

Interpretation and Conclusions. Our results suggest the usefulness of antiplatelet agents in the treatment of acute phase TTP patients. Moreover, a one-year ticlopidine maintenace therapy appears to be beneficial in preventing TTP relapses; however, only the completion of an adequate follow-up for all patients will definitively confirm this observation.

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Thrombotic thrombocytopenic purpura (TTP) is an uncommon hematologic syndrome in which microvascular platelet thrombosis produces a clinical picture characterized by thrombocytopenic purpura, schistocyte hemolytic anemia on a microangiopathic basis, fluctuating neuropsycological symptoms, fever and renal involvement.[1]

Until the late 1970's the prognosis of this disease was nearly always fatal.[2,3] Since then, however, plasma manipulation techniques – i.e. plasma infusion and plasma exchange – alone or combined with pharmacologic therapy, have allowed complete remission to be achieved in as many as 75% of treated patients.[3-5] Currently, plasma exchange must be considered the treatment of choice for TTP after having been proved superior to plasma infusion in a controlled clinical trial.[6]

Besides the problem of treating the uncommon forms of TTP resistant to plasma exchange,[7-9] another issue to be addressed is the effectiveness of all the drugs which are often combined with plasma exchange, antiplatelet agents in particular.[10] The rationale for the use of antiplatelet agents lies in the main pathologic feature of TTP – i.e. the presence of platelet thrombosis in the arterioles and capillaries of several organs and systems[11] and the evidence for platelet activation.[12] However, no definitive conclusions can be drawn on the actual

effectiveness of different antiplatelet agents based only on the single case reports and small retrospective studies reported in the literature, mostly because in the overwhelming majority of cases many protocols were combined.[13]

Even though in some cases antiplatelet agents (especially aspirin and dipyridamole) were reported to actually help disease remission,[14] in most cases no benefit came from the administration of these drugs.[13] Furthermore, some authors report a worsening clinical picture, especially as far as bleeding is concerned, after the pharmacologic inhibition of platelet function,[15] or even the onset of an acute TTP episode in some patients receiving ticlopidine,[16] an antiplatelet agent other authors consider to be an extremely promising tool.[17] Thus, antiplatelet agents are usually not recommended in TTP, especially when bleeding is observed in the central nervous system and/or the digestive system,[9,13,18,19] but in fact this thorny issue is still widely debated.

The Italian Cooperative Group for TTP carried out a randomized clinical trial to investigate the actual effectiveness of antiplatelet agents combined with plasma exchange and corticosteroids in acute TTP. In addition, the hypothesis was tested that manteinance treatment with antiplatelet agents could prevent possible TTP recurrence.

Patients and Methods

Inclusion criteria

Patients with an initial diagnosis of TTP referred to the different centers participating in the Italian Cooperative Group for TTP from September 1988 to December 1993 were considered for enrollment in the treatment protocol. The diagnosis of TTP was confirmed in the presence of the following findings: thrombocytopenia (< 100×10^9/L), microangiopathic hemolytic anemia (with schistocytes in peripheral blood smears, high LDH and low haptoglobin levels), no other possible causes of anemia and thrombocytopenia, neurologic symptoms and/or signs of altered renal function. Bone or gingival biopsies to demonstrate typical PAS-positive platelet thrombosis were not mandatory for a TTP diagnosis. Moreover, each patient gave his/her informed consent upon enrollment; when the patient was in a coma or suffered severe neurologic changes prejudicing discernment, informed consent was given by the closest relative.

Randomization

To enroll a new patient, the referring clinician asked the National Trial Coordinator to randomize him/her according to a given allocation table.

Treatment protocol

Patients were randomized to two arms; arm A patients received combined plasma exchange and methylprednisolone (2 mg/kg/day, i.v.), while arm B patients received both the above combination and antiplatelet agents (i.e. acetylsalicylic acid per os or lysine salicylate i.v., 10 mg/kg/day, plus dipyridamole, 3 mg/kg/day per os or 0.4 mg/kg/day i.v.). Plasma exchange was scheduled on a possibly daily basis, minimum 7 to maximum 10 sessions – at least 7 of them in the first 10 days – and, if complete remission was achieved, 2 more sessions were scheduled. Plasma exchange was performed by substituting one volume of patient plasma with the same amount of fresh frozen plasma from healthy donors; no albumin was used in the reinfusion fluid. Plasma collection and the tests on plasma itself, to exclude contamination by infectious agents, were always carried out according to the ever-evolving guidelines of the Italian government.

Fifteen days after treatment was started, disease status – i.e. complete/partial remission or no response – was assessed according to the following criteria: platelet count > 150×10^9/L, reticulocytes < 100×10^9/L, LDH < 300 U/L, serum BUN < 50 mg % and creatinine < 1.2 mg% for complete remission and platelet count > 100×10^9/L, but < 150×10^9/L, with LDH < 300 U/L for partial remission. As for non-responders, each clinician was totally free to choose a salvage treatment among the therapies known to be more or less effective in plasma exchange-resistant TTP, e.g. vincristine,[20] PGI$_2$,[21] high-dose IgG,[22] splenectomy.[3] In the case of partial remission, 7 more plasma exchange sessions were scheduled and, if complete response failed to be achieved, the patient was given high-dose IgG (0.4 g/kg/day, for 5 days).

Then, if complete remission was still not achieved yet, the patient was considered to be a non-responder and was treated as reported above. When complete remission was achieved, the patients treated with antiplatelet agents in the acute phase were scheduled to receive one-year maintenance treatment with ticlopidine (500 mg/day, per os), while those not treated with antiplatelet agents in the acute phase were scheduled for no additional therapy. The treatment protocol schedule is summarized in Figure 1.

Follow-up

The follow-up of complete remission patients is still in progress; the schedule calls for a clinical examination, including complete hemochromocytometric test, a peripheral blood smear and LDH titer, once a month for 6 months and then 3 times a year for the remaining 4 $\frac{1}{2}$ years. To unquestionably differentiate actual TTP relapses from new onsets due to early treatment discontinuation, we considered a relapse to be every episode which occurred after the platelet count had been maintained above 100×10^9/L for at least 4 weeks after therapy was stopped.[23]

During both the acute and the ticlopidine maintenance treatments (see above for details on the latter) special attention was paid to detecting any signs or symptoms of toxicity referrable to antiplatelet agents (and cortisone) in terms of new hemorrhages or a worsening of previous ones.

Statistical analysis

Fleiss' equation[24] was used to calculate the number of patients needed for initial enrollment to be 90% sure (β = .1, test potency = .9) of finding, when present, a 10% statistically significant difference (α = .05) between the response rates in the two treatment arms. The number thus calculated amounted to 336 patients, an unrealistic goal because TTP is a very uncommon disease; indeed, the Italian Cooperative Group for TTP has collected extensive data on no more than a hundred TTP cases in nearly 20 years' activity.

Therefore, considering that major information could nevertheless be gained, we chose to sacrifice statistical significance and set only a time limit.

Data were elaborated with the χ^2 test.

Results

Patient characteristics

In all, 72 patients were enrolled in this treatment protocol within the scheduled 6 years; 25 of them were men and 47 women, mean age (± SD) being 39.56 years (± 15.41) for men and 37.26 (± 15.72) for women.

At onset, all patients presented thrombocytopenia, with a mean platelet count of 22.202± 15.41×10^9/L (range: $4-81\times10^9$/L) and microangiopathic anemia, with a mean hemoglobin level of 7.94±2.02 g/dL (range: 4-11.7 g/dL); schistocytes
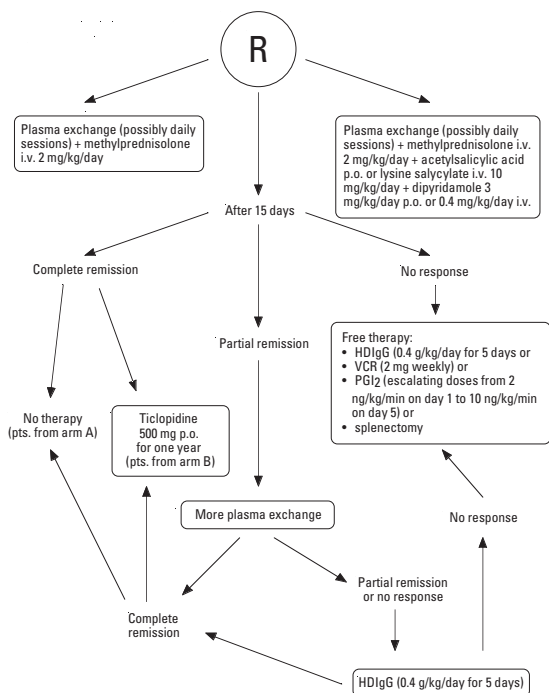
Figure 1. Summary of treatment protocol schedule.

were demonstrated in all cases. On admission, 59 patients presented with neurologic symptoms of varying severity (81.9%), 58 bleeding (80.5%) and 38 bio-humoral signs of altered renal function (52.7%).

As far as renal impairment in our TTP patients is concerned, a diagnosis of HUS (hemolytic-uremic syndrome) was arbitrarily ruled out since in all patients with kidney damage stool examination led us to exclude the presence of enterotoxins producing *Escherichia coli* strains; furthermore, in all cases, the clinical picture was predominantly characterized by the above mentioned non-renal manifestations.

Besides elevated creatinine and BUN levels, other common signs of renal impairment were the presence of hematuria (micro- or macrohematuria) and of cylindruria at urinanalysis. However, in the analysis of our patients, we included macrohematuria with the other types of bleeding.

These latter were mucocutaneous hemorrhages or macrohematuria in most patients (35 of 58 and 21 of 58, respectively), gastrointestinal bleeding in 8 and nervous system bleeding in 2 patients only. Eight patients had associated mucocutaneous hemorrhages and macrohematuria.

Patient randomization to the two treatment arms

Thirty-seven of the 72 patients were randomized to arm A and thus treated with combined plasma

exchange and methylprednisolone; the remaining 35 patients, randomized to arm B, received the above combination plus antiplatelet agents.

The demographic, bio-humoral and clinical features of the patients in our series are summarized in Tables 1 and 2; the two treatment groups appear well matched and statistically homogeneous. No statistically significant changes were observed between the two treatment arms relative to plasma exchange scheduling; thus, the average volume of plasma exchanged in each session was 2825 cc (± 300 SD) in group A and 2800 cc (± 350 SD) in group B (p = n.s.). Furthermore, the plasma exchange session/days ratio (in the first 15 days), whose prognostic value is well known,[5] was on the average .75 in group A and .7 in group B (p = n.s.).

Treatment efficacy

Independent of the type of treatment received, 60 patients (83.3% of the whole series) achieved complete remission, while 12 patients failed to respond and died (16.7%). Specifically, 28 complete remissions (75.6%) were achieved in arm A (plasma exchange plus methylprednisolone) vs. 32 (91.4%) in arm B (plasma exchange, methylprednisolone and antiplatelet agents); this difference was not statistically significant.

Considering disease state at 15 days, that is when treatment effectiveness was first assessed, 22 complete remissions (59.4%) were observed in arm A and 21 (60%) in arm B; in all, 43 patients were cured in 15 days of treatment. Once again, no statistically significant differences were observed. While no partial remissions were recorded, 6 patients died in the first 15 days – 5 in arm A (13.5%) and one in arm B (2.8%).

As for the above death rate, even though the difference between the two arms was not statistically significant (p = .073), the higher number of deaths in the group treated without antiplatelet agents

Table 1. Main demographic and biohumoral features of patients in arms A (#37) and B (#35).

	Overall mean	arm 'A' mean	arm 'B' mean	p
Patient age (years)	38.06	36.8	39.3	n.s.
Men's age (years)	39.56	38.3	41.1	n.s.
Women's age (years)	37.26	35.9	38.5	n.s.
Platelets (n.v. 150-400 x 10⁹/L)	22.2	23.5	20.9	n.s.
Hemoglobin (n.v. 12-17.5 g/dL)	7.9	8.03	7.83	n.s.
LDH (n.v. 100-225 U/L)	2210	2345	2074	n.s.
Serum BUN (n.v. 10-50 mg/dL)	63.5	66.4	60.2	n.s.
Creatinine (n.v. 0.3-1.2 mg/dL)	1.56	1.65	1.44	n.s.
Tot. bilirubin (n.v. 0.1-1.2 mg/dL)	2.91	2.85	2.97	n.s.

seems to suggest that these agents are useful in acute TTP. Of the 23 patients (10 from arm A and 13 from arm B) who did not respond at 15 days and were therefore submitted to free therapy, 17 (6 from arm A and 11 from arm B) achieved complete remission thanks to salvage therapy, while the other 6 (4 from arm A and 2 from arm B) died; in all, our death rate was 16.7%, which is in substantial agreement with the literature data.

The data relative to the types of free therapy and their results are summarized in Table 3. However, an analysis of salvage therapies and their results allows no unquestionable conclusions to be drawn.

Side effects of antiplatelet agents

One of the potential risks of using antiplatelet agents in acute TTP is that bleeding, which is so dramatically common in TTP, may worsen. In our personal series, we found no major evidence of this legitimate concern: during acute treatment, pre-existing bleeding worsened transiently in only 4 (11.4%) of the patients receiving antiplatelet agents (mucocutaneous bleeding in 3 and gastrointestinal bleeding in 1 patient). These symptoms regressed promptly and the overall clinical pattern normalized, with no lethal hemorrhages or bleeding so strong as to render the patient severely anemic.

Table 2. Main clinical features of patients in arms A (#37) and B (#35).

	Arm 'A'		Arm 'B'		
	# pts.	(%)	# pts.	(%)	p
Bleeding	30	(81.08)	28	(80)	n.s.
Neurologic symptoms	30	(81.08)	29	(82.8)	n.s.
Fever	20	(54)	20	(57.1)	n.s.
Renal signs	20	(54)	18	(51.4)	n.s.
Hepatomegaly	6	(16.2)	6	(17.1)	n.s.
Splenomegaly	2	(5.4)	3	(8.5)	n.s.
Hepato-splenomegaly	4	(10.8)	7	(20)	n.s.

Table 3. Salvage treatments and their results in 23 non-responders, according to the treatment arm the patients had been randomized to. No patient received more than one salvage treatment.

Salvage treatment	Arm 'A' (#10)		Arm 'B' (#13)	
	in remission	dead	in remission	dead
Splenectomy	0	2	—	—
Vincristine	2	1	6	0
PGI$_2$	1	0	2	1
High-dose IgG	3	1	3	1
Total # of pts.	6	4	11	2

Moreover, none of the non-bleeding patients exhibited any bleeding episode which could be related to the treatment.

Finally, regarding ticlopidine maintenance treatment, severe erosive gastritis appeared in two patients only (6.25%) and resolved with adequate medical therapy.

In neither the acute phase nor the maintenance period did any of the patients originally randomized to receive antiplatelet agents refuse treatment or need to discontinue it due to toxic effects.

Maintenance treatment efficacy

Of the 60 patients who achieved complete remission, 32 were given ticlopidine as maintenance treatment for one year, while the 28 not treated with antiplatelet agents in the acute phase received no maintenance therapy and were considered as a control group.

Currently, after all these patients have completed their maintenance treatment, 8 (13.3%) have relapsed: 2 (6.25%) in the ticlopidine group and 6 (21.4%) in the non-ticlopidine group. The two relapses in the treated group were observed 18 and 30 months, respectively, after the acute TTP episode. In contrast, the 6 controls relapsed at 12.1 months on the average (range: 4-20), with as many as two patients having a recurrence within 6 months of the acute episode.

The intergroup difference rate is, at present, statistically significant (p = .0182) in favor of the ticlopidine group. However, no definitive conclusions can be drawn before follow-up is completed for all patients. As for tolerance, ticlopidine treatment was completed in all the patients scheduled to receive it and the drug caused no clinically important side effects.

All relapsed patients were successfully retreated with plasma exchange, steroids and antiplatelet agents, used at the above dosages and with the reported modalities.

Discussion

Plasma exchange is the treatment of choice for TTP patients and, since it has proven to be superior to plasma infusion alone,[7] this technique can be hypothesized to act primarily by removing some disease-causing factor rather than by replacing a missing one. Indeed several reports suggest the existence of one or more factors causing the abnormal platelet aggregation typical of TTP: for instance, class-G antibodies,[25] a small protein,[26] unusually large von Willebrand factor (vWF) multimers,[27] a cysteine-proteinase,[28] etc.

In all these cases, the apheretic component of plasma exchange is reported to remove the involved factor, while replacing the patient's plasma with fresh frozen plasma from healthy donors is reported to help restore normal plasma inhibitory

action.[29] Moreover, plasma exchange is reported to stimulate prostacyclin production,[30] to lengthen its activity,[31] or to support the conversion of abnormally large vWF multimers into smaller, nonpathogenous forms.[32]

However, besides plasma exchange or infusion, several drug treatment protocols have often been used not only because the actual etiopathogenetic mechanism underlying the protean clinical picture of TTP is still debated, but also because of the severity of TTP and, in some cases, because starting plasmapheresis early is difficult. In particular, steroids and antiplatelet agents are often combined with conventional plasma manipulation techniques.

The rationale for using glucocorticoids is based on the historic observation that some TTP patients responded to corticosteroids alone[19] and, especially, on the assumption that TTP may have an autoimmune component, in which case the possible production of autoantibodies against endothelial cells or ultralarge vWF depolymerase[27,33,34] would be inhibited by cortisone administration.

Even though these suppositions are aleatory, steroids are so commonly combined with plasma exchange that Moake suggests administering them (0.75 mg/kg methylprednisolone, i.v., every 13th hour) as soon as TTP is diagnosed.[35]

Using antiplatelet agents seems to be a more rational choice, since the main pathologic feature of TTP is the presence of platelet thrombosis in the microcirculation.[11] Nevertheless, many renowned authors have spoken against antiplatelet agents,[9,13,18] even though the issue is still debated.

For instance, as Rock reports in her fundamental paper,[7] in Canada combining aspirin and dipyridamole with plasma exchange is considered an essential step in TTP treatment.

The main objection to antiplatelet agents in acute TTP is that they may worsen or support bleeding, which is at any rate a typical feature of the clinical picture of TTP. This concern, put forth mainly by Rosove in 1979,[15] made Phillips suggest that antiplatelet agents not be used when bleeding is observed in the central nervous system and/or gastrointestinal system.[13] Furthermore, literature reports surely do not help clarify the issue because some authors come out in favor of[14,17] and some against[15,16] antiplatelet agents, the results being affected most often by the fact that many different treatment protocols are frequently combined.[13]

To address this complex issue, the Italian Cooperative Group for TTP has activated a national treatment protocol to investigate the actual effectiveness of antiplatelet agents in TTP.

Even though statistical significance could not be attained, our results suggest that antiplatelet agents are rather innocuous in acute TTP. The response rates in our two treatment arms are much

the same – or even slighty higher in the antiplatelet arm; moreover, when aspirin and dipyridamole were added, bleeding did not worsen. In fact, lower mortality rates at 15 days in the patients treated with antiplatelet agents (1 death only vs. 5 in the treatment arm without antiplatelet agents), although not statistically significant, would seem to suggest that these agents might even be useful when combined with plasma exchange and steroids, to prevent deaths in acute TTP.

In an attempt to distinguish responders from non-responders in terms of prognostic factors, we applied Rose and Eldor's severity score to our case-series;[36] unfortunately, this scoring system, based on four clinical and laboratory parameters (neurological findings, renal function impairment, platelet count and hemoglobin value at presentation), did not allow us to identify any relevant prognostic factor (p=n.s.).

In our opinion, the use of combined aspirin and dipyridamole in the acute phase, plus ticlopidine as maintenance treatment, is worth discussing in detail.

Aspirin is known to act on platelets through irreversible acetylation of cyclooxygenase, resulting in totally impaired prostaglandin production from arachidonic acid, and on endothelial cells by inhibiting endothelial cyclooxygenase, with consequent totally impaired PGI_2 production,[37] which accounts for its use in several thrombotic disorders. As far as the dose of aspirin used in our study is concerned, at the time the protocol was designed there was considerable speculation about the dose needed to inhibit platelet function *in vivo*, and particularly in a disease such as TTP, which is characterized by rapid platelet turnover. A single 50 mg dose of aspirin taken orally by an adult was known to be sufficient to prolong bleeding time and severely depress the amount of TXA_2 metabolites excreted in the urine; however, the dose required to inhibit the generation of PGI_2 was thought to be higher.[38] This is why we chose such a high dose of aspirin.

The use of dipyridamole in TTP is even more debated. Indeed, even though this agent is reported to increase the intraplatelet concentration of cyclic adenosine monophosphate, this effect is not apparent at drug doses which can be obtained physiologically.[13] Therefore dipyridamole is used in TTP and other conditions[39] based on the results of old, nonrandomized literature reports. Thus, just like the Canadian group, we chose to include it in our protocol based on a temporal relationship between its administration or dosage increase and disease remission, as reported by many authors.[13]

As for ticlopidine, it was reportedly a very promising drug, even though its mode of action was not completely known, when we planned our protocol;[10] moreover, none of the reports on TTP onset

in ticlopidine-treated patients which drew so much attention some years later[16] had been published yet, while some positive experiences with this drug were reported in the literature.

So, for maintenance treatment our results seem to support ticlopidine administration for a year after remission; indeed the current relapse rate is markedly higher in non-ticlopidine-treated than in ticlopidine-treated patients. Even admitting that our study design does not exclude the possibility that the initial treatment with aspirin and dipyridamole may account for the advantages observed after maintenance treatment, the role of antiplatelet agents nevertheless seems unquestionable. This important observation must of course be confirmed by a longer follow-up of all patients, especially because of the high rate of late relapses observed in the Canadian series.[23] However, since early relapses appear to be much more frequent in Italy than in Canada[40] for reasons we cannot fully understand yet on the basis of our current biologic knowledge of TTP, the efficacy of maintenance treatment in preventing disease relapse observed in our study remains equally significant.

To conclude, our results suggest that antiplatelet agents combined with indispensable plasma exchange (and steroids) are definitely not contraindicated in the treatment of TTP, but may even protect the patients receiving them, thus – perhaps – decreasing mortality in the acute phase. This beneficial effect is even more apparent when considering the results of maintenance treatment with ticlopidine; however, only the completion of an adequate follow-up for all patients will unquestionably confirm this observation.

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Appendix

Centers adhering to the Italian Cooperative Group for TTP:

Divisione di Ematologia, Ospedale Generale, Bolzano (O. Prinoth), Unità di Ematologia, Ospedale Santa Chiara, Trento (M. Rubertelli), Centro Trasfusionale, Ospedale Civile, Padova (G. Ongaro), Divisione di Ematologia, Ospedale Civile, Vicenza (F. Rodeghiero), Servizio di Immunoematologia, IRCCS Policlinico San Matteo, Pavia (L. Salvaneschi and C. Perotti), Divisione di Nefrologia, Ospedale Niguarda, Milano (G. Busnach), Centro Trasfusionale, Ospedale Maggiore, Lodi (G. Cambiè), Istituto di Ematologia, IRCCS Policlinico San Matteo, Pavia (A. Canevari), Divisione di Ematologia, Ospedale Civile, S. Giovanni Rotondo (M. Carotenuto), Divisione di Ematologia, Ospedale Pugliese, Catanzaro (G. Leda), Servizio di Immunoematologia e Trasfusionale, Ospedali Riuniti, Sassari (G. Bertrand), Divisione di Ematologia, Ospedale Businco, Cagliari (A. Broccia), Divisione di Medicina V, Ospedale Regionale, Parma (D. Poli), Ospedale Servello, Palermo (A. Chimè), Servizio Trasfusionale, Policlinico Gemelli, Roma (G. Menichella), Servizio di Immunoematologia e Trasfusionale, Ospedale Civile, Pescara (A. Iacone), Istituto di Ematologia "L. & A. Seragnoli", Università di Bologna (L. Gugliotta, N. Vianelli), Dipartimento di Medicina Interna e Nefrologia, IRCCS Policlinico San Matteo, Università di Pavia (C. Porta), Istituto di Medicina Interna e Oncologia, IRCCS Policlinico San Matteo, Università di Pavia (E. Ascari, *National Coordinator*), Centro Trasfusionale, Ospedale di Careggi, Firenze (G. Avanzi), Servizio di Immunoematologia e Trasfusionale, Ospedale Santa Chiara, Pisa (P. Fosella), Divisione di Ematologia, Ospedale S. Camillo, Roma (N. Petti), Divisione di Medicina, Ospedale Civile, Borgo Sesia (L. Anselmetti), Sezione di Ematologia, Università di Roma (G. Isacchi), Istituto di Clinica Medica, Università di Ancona (R. Centurioni), Servizio Trasfusionale, Ospedale Cardarelli, Napoli (C. Vacca), Banca del Sangue, Ospedale S. Giovanni Battista, Torino (F. Peyretti), Divisione di Medicina B, Ospedale Civile, Biella (M. Antonini), Servizio Trasfusionale, Ospedale Galliera, Genova (R. Adami), Divisione di Ematologia, Policlinico, Modena (U. Di Prisco), I Divisione di Medicina Generale, Arcispedale S. Maria Nuova, Reggio Emilia (L. Masini), Divisione di Medicina Generale, Ospedale Maggiore, Crema (E. Bobbio-Pallavicini, *Group Responsible*, and F. Tacconi).