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Thrombotic thrombocytopenic purpura treatment in year 2000

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ABSTRACT

Background and Objectives. **For several decades clinicians worldwide considered TTP a severe and frustrating therapeutic problem. Fortunately, however, the prognosis of TTP patients has greatly benefited from the use of plasma manipulation techniques, particularly plasma-exchange (PE), so that the overall rate of complete responses currently ranges between 70-85% and may even exceed these figures. Despite this dramatic improvement, a number of questions remain concerning the best treatment for TTP patients. Analyzing acquired data and discussing future perspectives, this review will address the following key issues: 1) is PE really the treatment of choice for TTP and what is the role of PE with cryosupernatant? 2) what is the role of all the drugs which are commonly combined with PE, antiplatelet drugs and steroids in particular? 3) what, if any, is the role of cytotoxic agents, especially vincristine? 4) is there a treatment for PE-resistant patients? 5) does secondary TTP need different treatments?**

Design and Methods**. The authors have been involved in the study and treatment of TTP for years; furthermore, they extensively searched the PubMed database of the National Library of Congress through the Internet.**

Interpretation and Conclusions. **PE remains the treatment of choice for TTP. A large randomized trial now in progress will assess whether exchange with cryosupernatant plasma can improve treatment efficacy. The administration of antiplatelet drugs in combination with PE was fiercely debated over the past years but seems indicated both in acute TTP and as a prophylactic treatment to prevent relapses. It appears that steroids cannot be avoided, especially in light of the latest findings on TTP pathogenesis, but only specific trials will assess the optimal cortisone type and dose. Presently, different treatments can be suggested only to patients failing to respond to PE, while no specific therapy can be indicated for secondary TTP, which usually has a very poor prognosis. Finally, we would like to stress that only international cooperative (multicenter) trials on large series of patients will be able to shed light on a still obscure, if fascinating, disease. Our hope and wish is that the new century will see TTP among the diseases defeated by man's clever mind and heart.**

Key words: TTP, treatment, review, plasma-exchange, antiplatelet drugs, steroids

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Thrombotic thrombocytopenic purpura (TTP) is an uncommon hematologic syndrome. It was first described by Dr. Eli Moschowitz in 1924, but the term TTP was introduced by Karl Singer over twenty years later.[2]

TTP is currently estimated to occur in about 1 case per million people,[3] with a preference for young women in their thirties, but the trend seems to be on the increase.[4]

The clinical presentation of TTP results from occlusive microangiopathy preferentially localized to terminal arterioles and capillaries – but not venules – throughout the whole body. Signs consist of microangiopathic schistocytic hemolytic anemia, consumptive thrombocytopenia causing severe hemorrhagic diathesis, fluctuating central nervous system abnormalities, fever and renal impairment of different degrees,[1] but the classic pentad of the above symptoms is seen in only about 40% of patients. In contrast, the triad of anemia, thrombocytopenia and bizarre neurologic abnormalities can be observed in as many as 75% of patients,[3] which suggests that TTP should be redefined as a syndrome of Coombs' negative microangiopathic hemolytic anemia and thrombocytopenia in the absence of any other possible causes of these manifestations.[5,6]

The formation of platelet aggregates is the key pathogenic feature of TTP, but their etiology remains elusive. Several recent studies indicate an abnormal interaction between damaged vascular endothelium and platelets,[7] while other investigators reported different platelet aggregating plasma proteins of the family of cysteine proteinases.[8-11] In fact, several experimental findings support the concept of endothelial damage, namely: the abnormal production and metabolism of von Willebrand factor (vWF) multimers, with ultra large vWF multimers capable of increasing platelet adhesiveness *in vitro*, shed into the

circulation by endothelial cells,[12] reduced vascular prostacyclin (PGI_2) production,[13] impaired fibrinolytic activity,[14] increased vascular endothelial cell markers in blood,[15] and pro-apoptotic effects of TTP plasma on microvascular endothelial cells *in vitro*.[16] More recently, the hypothesis of an autoimmune origin of TTP has regained strength and support.[17] Two papers, by Tsai and Furlan, have recently described the presence of an antibody to a plasma protease in the serum of many TTP patients.[18,19]

Clinicians worldwide considered TTP a severe and frustrating therapeutic problem for several decades. In 1965 Amorosi and Ultman reviewed a series of 271 TTP patients and found that only 10% of them had survived the acute phase – most patients having died within 90 days of the onset of TTP symptoms.[20]

Fortunately, however, the prognosis of TTP patients has greatly benefited from the use of plasma manipulation techniques, particularly plasma-exchange (PE), so that the overall rate of complete responses currently ranges between 70-85% and may even exceed these figures.[6]

Nevertheless, some key questions about TTP treatment remain unanswered:

1. Is PE really the treatment of choice for this uncommon disease?
2. What is the role of PE with cryosupernatant, i.e., the fraction of plasma from which cryoprecipitate containing the largest vWF multimers, fibrinogen and fibronectin has been removed?
3. What is the role of all the drugs which are commonly combined with PE, antiplatelet drugs and steroids in particular?
4. What, if any, is the role of cytotoxic agents, especially vincristine (VCR)?
5. Is there a treatment for PE-resistant patients?
6. Does secondary TTP need different treatments?

Plasma-exchage with or without cryosupernatant

Up to the mid-60s TTP was considered an almost universally fatal disease. Then plasma infusion resulted in the first successful treatment which was attributed, at that time, to the fact that the plasma added a substance which inhibited the platelet aggregating factor and promoted endothelial healing.[21,22] Plasma exchange therapy rapidly followed based on the theory that removal of any (putative) toxic agent might have an additive effect to plasma infusion. This was based on the relatively obscure pathogenesis of TTP, which was then thought to result from one or a combination of:

1. a PGI_2 or PGI_2-precursor deficiency,
2. immunologic mechanisms such as:
   a) circulating immune complexes,
   b) antiplatelet antibodies,
   c) an endothelial cytotoxic factor,
3. the presence of a platelet aggregating factor, or
4. abnormalities of von Willebrand factor.

A Canadian Apheresis Group study in 1991 confirmed the superiority of fresh frozen plasma exchange over fresh frozen plasma infusion with 49% response after 7 days and 78% survival at one month with exchange compared to 25% and 63%, respectively, with infusion.[6] In that study patients received 1.5 plasma volume (PV) exchanges for the first 3 days followed by four 1 PV exchanges over 6 days or 30 mL/kg plasma infusion over the first 24 hours followed by 15mL/kg daily until the end of the treatment cycle. The results supported the concept that plasma exchange was not only providing the deficient substances in those suffering the microangiopathy but also removing toxins and/or clot promoting factors from the patient's plasma.

However, a considerable mortality persisted. Fresh frozen plasma contains von Willebrand factor and high molecular weight multimers of vWF have been implicated in the pathogenesis of TTP.[19] Specifically, in patients with chronic relapsing forms of the disease ultra high molecular weight (UHMW) forms of vWF have been reported. Moake[23] has shown that such UHMW forms have an enhanced ability to cause platelet aggregation, particularly under conditions of high shear stress. Variable reports of UHMW forms have been made for patients suffering single-episode TTP. Therefore it was suggested that cryosupernatant plasma, which is relatively depleted of the high molecular weight von Willebrand factor multimers, might be a better replacement solution for patients with TTP.[24] In a *Canadian Apheresis Group* pilot study, 18 patients with TTP who failed to respond to an initial treatment cycle (7-9 days) with fresh frozen plasma were treated with cryosupernatant. The 83% response rate led to the use of cryosupernatant in 40 new TTP patients and resulted in 95% one-month survival in comparison to the 78% survival rate reported in our original study.[25] Thus, we hypothesized that plasma exchange with cryosupernatant provides the host with the plasma products which inhibit the aggregating factor while being deficient in the high molecular weight multimers of von Willebrand factor which contribute to the platelet microthrombi. The encouraging results from our uncontrolled studies and the relative difficulties which many centers experience in obtaining cryosupernatant plasma indicate the necessity of carrying out a controlled, prospective study to compare these two replacement solutions. Such a study is currently under way in Canada and several other countries. Hopefully, the results will provide definitive direction for future treatment of this disease.

Another possible replacement fluid is solvent/detergent-treated plasma (SDTP). This is pooled plasma that has been treated with a combination of an organic solvent and a detergent to inactivate viruses. The process effectively inactivates lipid encapsulated viruses including hepatitis C and HIV. It is not effective against non-lipid organisms such as parvovirus and hepatitis A. Moake *et al.*[26] have reported on the successful use of SDTP in the treatment of some patients with TTP. The solvent/detergent process has been said to alter the usual plasma vWF multimer pattern with loss of some of the higher molecular weight multimers of vWF.[27] As discussed above, the UHMW vWF multimers are considered to enhance platelet adhesion under conditions of high shear stress.[23] Therefore, at least in theory, use of SDTP, with a lower level of HMW vWF multimers might not only avoid the risk of exposure to some of the common viruses

but might also provide benefit in reducing the exposure to HMW vWF. Again, controlled clinical trials are necessary to determine whether SDTP is at least as efficacious as fresh frozen plasma (FFP) during PE to treat TTP. Because PE with FFP has proven to be of benefit in reducing the mortality rate to approximately 20% in this previously highly lethal disease, it is critical that any other replacement fluid used be at least as good. At present, the appropriate prospective randomized clinical trials are yet to be done.

Recently, two papers by Tsai and Furlan[18,19] have followed-up on their earlier observations concerning the activity of another protease which acts to convert high molecular weight von Willebrand factor to subunits of 150 and 200 kD. Both investigators suggest that it is the action of this protease which, by decreasing the molecular weight of von Willebrand factor, reduces its proclivity to bind to platelets and cause agglutination, particularly under conditions of high shear stress. Tsai found that 26 out of 39 patients had an inhibitor to this protease in their plasma at the time of presentation. Furlan also found an IgG fraction in the plasma of many patients with TTP which inhibited the action of this protease. It is a hypothesis of these two papers that TTP is a disease in which an inhibitor to the protease permits the survival in the circulation of very high molecular weight forms of von Willebrand factor which have an increased capacity for binding to platelets and causing aggregates. The assay for this protease is based on incubation with high molecular weight von Willebrand factor in the presence of non-physiologic concentrations of urea and barium. In Tsai's work the production of bands at 300 kD following PAGE-electrophoresis was inversely correlated to the level of inhibitor activity. This provided some exciting impetus to further study; most of the sera studied by these two groups were from stored samples and the patients were not followed-up in a prospective fashion. So it will be extremely important to prospectively follow-up a group of TTP patients who undergo appropriate current therapy to determine the levels of protease and inhibitor activity throughout treatment and the effects of the two replacement fluids on these levels.

In this regard it should be noted that the presenting biochemical and hematologic parameters for a total of 145 TTP patients were described in a recent article by the *Canadian Apheresis Group.*[28] Patient's blood was collected directly into citrated glass tubes and not exposed to the plastic apheresis tubing. Nonetheless the pattern of von Willebrand multimers did not consistently show the presence of very high molecular weight multimers. Rather, there was an approximately equal distribution between high, normal and reduced multimer patterns. Thus the specific role of the ultra high molecular weight von Willebrand factor and its interaction with protease requires clarification.

In conclusion, the already stressed need for controlled, multicenter, randomized clinical trials aimed at exploring the best treatment options for TTP and, particularly, the best PE protocols, makes it difficult to identify the ideal PE procedure, at least at present. PE guidelines elaborated by the *Canadian Apheresis Group* for an ongoing clinical trial are reported in Table 1; these guidelines have also been accepted by the *Italian Co-operative Group for TTP* and will be used within the upcoming Italian multicenter clinical trial.

Table 1. Recommendations for PE treatment of TTP acute phase according to the *Canadian Apheresis Group*.

- Apheresis treatment is to consist of daily 1.5 plasma volume exchanges on the first two days of treatment, then single volume plasma exchange, with either cryosupernatant plasma or fresh frozen plasma as replacement fluid.
- Even though specific data concerning the use of albumin as a replacement fluid in TTP patients are lacking, its use is usually discouraged due to well known data indicating a decremental effect of this substance on overall survival of critically ill patients.

Drugs which are commonly combined with plasma exchange: antiplatelet drugs

Of the several drugs which are usually combined with PE to treat TTP patients, antiplatelet drugs are surely among the most common (Table 2), according to our literature survey.

The rationale for the use of antiplatelet agents lies in the main pathologic feature of TTP – i.e., the presence of platelet thrombi in the arterioles and capillaries, but usually not the venules, of several organs and systems in TTP patients.[29,30]

Despite their widespread use, it is extremely difficult to judge the actual effectiveness of these agents based only on the single case reports and small retrospective studies found in the literature, mostly because in the overwhelming majority of cases many treatment modalities – including PE – were combined.[31]

Acetylsalicylic acid (ASA) and dipyridamole

ASA is probably the most widely used antiplatelet drug in the world. It acts both on platelets through the irreversible acetylation of a serine residue of the enzyme cyclo-oxygenase (COX), resulting in totally impaired prostaglandin production from arachidonic acid, and on endothelial cells by inhibiting endothelial COX, with consequent totally impaired PGI_2 production.[32] As for its action on platelets, the effect persists throughout the life of the platelet, thus affecting thrombocyte function and bleeding until new platelets are released from the bone marrow into the blood stream.[33] Long-term administration of doses higher than 2 g/day also decreases synthesis of vitamin K-dependent factors (factors II, VII, IX and X) and prolongs the prothrombin time.[34] Moreover, salicylate metabolites derived from ASA hydrolysis may increase plasma fibrinolytic activity.[35] High ASA doses reportedly inhibit both thromboxane A_2 (TXA_2) and PGI_2 synthesis,[36] thus defining a potential prothrombotic effect,[37] although this effect has never yet been studied.

The role of dipyridamole in the treatment and/or prevention of thrombosis is debated more frequently. Originally used as a vasodilator, dipyridamole displays an antiaggregating activity mostly consisting of phos-

Table 2. Antiplatelet agents used to treat TTP patients, according to our literature survey. At present, only ASA and dipyridamole are commonly used (usually in combination), while the role of ticlopidine is highly controversial (see text). Defibrotide appears to be a promising drug, while dextran and sulfinpyrazone should be considered as historical curiosities. As for epoprostenol (more precisely a PGI_2 analog and not an antiplatelet drug), data supporting its use in TTP are scarce and at present inconclusive.

Drug	*Suggested mechanism of action*	*Dose used to treat TTP patients according to the literature*
ASA	Inhibits cyclo-oxygenase	300-3900 mg
Dipyridamole	Inhibits phosphodiesterase; increases adenosine plasma levels	400-600 mg
Ticlopidine	Inhibits ADP-induced platelet aggregation and fibrinogen binding	500-1000 mg
Dextran	Inhibits the reaction of vWF with glycoprotein (Gp) Ib	10-15 mL/kg/day
Sulfinpyrazone	Inhibits cyclo-oxygenase competitively	800 mg
Defibrotide	Increases PGI_2; shows fibrinolytic and antithrombotic activity	10 mg/kg
Epoprostenol	Acts as natural prostacyclin (PGI_2)	Increasing doses, from 2 ng/kg/min to 10 ng/kg/min in 5 days, by continuous i.v. infusion

phodiesterase inhibition; an increased cAMP concentration has also been proposed,[38] but lately this effect has not been demonstrated at physiologically attainable concentrations of the drug. Furthermore, randomized clinical trials comparing dipyridamole with ASA or placebo have not proven any superiority of dipyridamole.[39] Indeed, the use of dipyridamole in thrombotic disorders is largely based on historical bias and precedent[31,39] and not on carefully performed randomized comparison studies. However, a temporal relationship between dipyridamole administration or dosage increase and disease remission in TTP patients has been reported by some authors,[31] leading to great – although probably unworthy – confidence in its usefulness, as we shall see later.

These antiplatelet agents – i.e., ASA and dipyridamole – have both been frequently administered, as single agents or in combination, to treat TTP patients, since the first report on the use of ASA by Jobin and Delage in 1970.[40]

Unfortunately, until recently, it was extremely difficult to draw definitive conclusions on their real effectiveness based only on single case reports or, at best, small and uncontrolled series published in the international literature. Also, quite invariably, several other treatment modalities (including highly-active plasma manipulation techniques) were also combined with antiplatelet agents to treat TTP patients, making it impossible to assess the effective role of these drugs. Thus, even though antiplatelet agents were reported to help in disease remission in some cases, in the majority of cases no benefit was derived from the administration of these drugs.[31] Moreover, some authors report a worsening of the clinical picture, especially in relation to bleeding, after pharmacologic inhibition of platelet function;[41] thus, antiplatelet agents were usually pronounced against in TTP, especially when bleeding was observed in the central nervous system and/or the digestive system.[22,31,42,43]

However, a recent randomized trial by the *Italian Cooperative Group for the Study and Treatment of TTP* has changed this point of view. Indeed, the results of the above randomized multicenter study suggested that the combination of ASA and dipyridamole (given at the dose of 10 mg/kg/day and 3 mg/kg/day *per os* or 0.4 mg/kg/day i.v., respectively) is rather innocuous in acute TTP, if bleeding does not worsen due to the pharmacologic impairment of platelet function. The response rate observed in the patients who received the antiplatelet agents as an adjunct to PE was identical to that of the PE-only arm of the study. Also, even though statistical significance was not attained, the lower mortality rate at 15 days observed in the patients treated with antiplatelet agents (1 death only, vs. 5 in the treatment arm without antiplatelet agents), would seem to suggest that ASA and dipyridamole might be useful, when combined with plasma exchange and steroids, in preventing deaths in acute TTP.[44]

Similarly, in the randomized trial by the *Canadian Apheresis Group*, which demonstrated the superiority of PE over plasma-infusion (PI), ASA and dipyridamole were given to acute phase TTP patients, with no evidence of any worsening of the hemorrhagic diathesis.[6]

In conclusion, these results seem to suggest that antiplatelet agents, combined with indispensable plasma exchange (and steroids), are definitely not contraindicated in the treatment of TTP[6,44] but may even protect the patients receiving them.[44] Finally, the potential role of ASA for relapse prophylaxis will be explored within an upcoming multicenter, controlled, randomized study by the *Italian Co-operative Group for TTP*.

Ticlopidine

Ticlopidine, a thienopyridine compound, alters platelet function by inhibiting the binding of adenosine-5'-diphosphate to its adenyl-cyclase-coupled receptor site; the drug decreases clottable fibrinogen but not the fibrinogen antigen, and decreases fibronectin. Its effect becomes apparent after repeated oral administrations and persists for up to 7-10 days after drug discontinuation, probably because one or more active metabolites is irreversibly bound to the

platelets.[45-47] Ticlopidine is being used more and more frequently to prevent stroke and clot formation after cardiac stent placement and as a treatment for *claudicatio intermittens*, in which conditions it proved to be effective within controlled, randomized trials.[48,49]

In 1984 Ishii *et al.* first reported on the effectiveness of ticlopidine in a TTP patient;[50] since then, other case reports and small series have appeared in the literature supporting the efficacy of this drug in the treatment of acute-phase TTP.[51] Because of these promising but early reports, in 1988 the *Italian Cooperative Group* included ticlopidine in its protocol, as maintenance treatment; ticlopidine was given at the dose of 500 mg/day *per os* for one year after complete remission had been achieved.[44] The recently published results of this study seem to support ticlopidine administration as maintenance treatment after remission, the observed relapse rate being significantly higher in the non-ticlopidine than in the ticlopidine-treated patients (21.4% vs. 6.25%, $p = 0.0182$). This holds true even considering that the study design did not exclude the chance that the initial treatment with ASA and dipyridamole might account for the advantages observed consequent to the ticlopidine treatment.[44]

To complicate the picture further, since ticlopidine was first marketed in the U.S. (October 1991), the *U.S. Food and Drug Administration* has received reports of ticlopidine-induced cases of TTP. Recently, Bennet *et al.*[52] reviewed all the cases of ticlopidine-associated TTP from different sources. The authors identified 60 patients who developed TTP during ticlopidine treatment; almost two thirds of them were males over 60 years old and 72% of them had received ticlopidine for stroke prevention. Ticlopidine had been prescribed for less than 2 weeks in 15% of patients and for less than 1 month in 80% of patients. The mechanism by which ticlopidine induces the clinical manifestations of TTP is still unclear. A metabolite of ticlopidine exerting a very different activity from the parent compound rather than the parent compound itself is thought to be responsible for the action.[52,53]

Despite the positive results from the Italian study, and the typically older age of the patients presenting such a strange side-effect of ticlopidine (very different from the typical age of onset of TTP), the large and still increasing number of ticlopidine-associated TTP cases suggests extreme caution in prescribing this compound. Indeed, the results of the maintenance arm of the Italian trial could be interpreted as an indication of the usefulness of antiplatelet drugs as a whole, instead of as an indication of the usefulness of ticlopidine *per se*.

Prostanoids

Prostacyclin (PGI_2), a strong natural inhibitor of platelet activation and aggregation acting at damaged vascular sites, has been related to the pathogenesis of both TTP and its close relative the hemolytic-uremic syndrome (HUS); as regards TTP, some experimental evidence supports the hypothesis of an accelerated PGI_2 degradation, even though we are far from any definitive conclusion on its actual implication in the pathogenesis of TTP.[54] Despite this uncertainty, the PGI_2 analog epoprostenol has been administered to TTP patients, with controversial results.[54] Whether the new prostanoid analog of PGI_2, iloprost (which has only recently been developed and is much more manageable than epoprostenol), will be useful for treating TTP patients, especially those resistant to PE-based treatments, remains to be investigated.

Drugs which are commonly combined with plasma exchange: steroids

If antiplatelet drugs are among the commonest drugs combined with PE to treat TTP patients, corticosteroids are undoubtedly the drugs most physicians use most systematically in addition to PE in the treatment of TTP, even though no one can say with certainty whether they are really necessary, simply useful or quite useless.[55]

Over the years, several hypotheses were used as rationales to support and justify the use of corticosteroids in TTP patients: Del Zoppo and Harker suggested steroids could be useful to inhibit a hypothetical generalized phenomenon of the Sanarelli-Schwartzman type[56] and Krause reported that steroids given at high doses may stabilize platelet and endothelial cell membranes.[57] Pisciotto *et al.* suggested that corticosteroids may at the same time inhibit macrophage activity and reduce the removal of IgG-sensitized platelets,[58] while Byrnes reported on an increase in the activity of T-suppressor lymphocytes, leading to inhibited antibody production.[59]

Indeed, the search for a suitable rationale for the use of steroids in TTP must consider this latter's pathogenesis, and it is quite obvious that the ideal indication for the use of steroids would be a condition with immunologic pathogenesis.

Over the years evidence has increased in favor of an autoimmune hypothesis for TTP pathogenesis; however TTP should not yet be considered an autoimmune disease. At present, autoantibodies should be regarded as only one of the many different insults which can trigger microvascular thrombosis.[17]

The literature survey is of little help in drawing any conclusion on the actual role of steroids in TTP treatment. Indeed, although the observation by Ridolfi and Bell that almost all the patients who survived TTP episodes had received prednisone[3] may leave us skeptical – it would also be justifiable to state that nearly all the patients who did not survive received steroids[55] – it is also clear that patients with less severe TTP recovered from their disease when treated with glucocorticoid therapy alone.[60]

At present, lacking a randomized study assessing the impact of corticosteroids on the prognosis of TTP patients[55] and not being able to rule out an underlying autoimmune mechanism before starting any treatment in the large majority of TTP patients, we subscribe to Moake's indications: unless glucocorticoids are contraindicated in an individual patient, it is probably advisable to start methylprednisolone immediately after diagnosis, combining it with prompt plasma-exchange, and to continue it until the patient recovers.[44,60,61]

The dose of methylprednisolone should vary little from that suggested by Moake[61] – i.e., 0.75 mg/kg i.v.,

every 12 hours (or prednisone orally at about 1.0 mg/kg) or that used in the Italian multicenter study[44] – i.e., 2 mg/kg/day, i.v. However, on the basis of the already mentioned experimental evidence supporting the autoimmune hypothesis for TTP pathogenesis, the use of higher doses of corticosteroids could also be considered; thus, the *Italian Co-operative Group for TTP* is presently activating a multicenter, randomized, controlled trial aimed at evaluating, together with other relevant topics, the effective role of high doses of steroids, in adjunct to PE and antiplatelet agents, in treating acute TTP patients.

The role of vincristine

Vincristine sulphate (VCR) is a strong immunosuppressant which is primarily administered as a single agent or in combination with other cytotoxic drugs to treat several hematologic and solid neoplasms. It was also used to treat different types of thrombocytopenia, such as ITP and secondary thrombocytopenias,[62] after the clinical observation of the frequent occurrence of thrombocytosis in VCR-treated cancer patients.[63] In fact, VCR is the only antimitotic compound which has no toxic effects on marrow megakaryopoiesis.[63]

To date, the reported action of VCR in thrombocytopenias, and TTP in particular, has not been unequivocally explained, since several hypotheses have been offered.

First, VCR is reported to alter glycoprotein receptors on the platelet surface in a process similar to that of the disassembly of the microtubules of the mitotic spindle by which it acts as an anticancer agent; this would prevent attachment of vWF multimers and therefore reduce platelet aggregation.[64]

Second, VCR is thought to cause immunomodulation at the endothelial wall,[65] an action which seems central in TTP; Burns reported that endothelial cells exposed *in vitro* to plasma from TTP patients are damaged by IgG-type antibodies,[66] and that the use of VCR prevents this phenomenon.[64]

Other studies of the effects of VCR on endothelial cell barriers (such as the blood-brain barrier),[67] and on the effects of other anti-tubulin drugs on the endothelium,[68,69] suggest that other mechanisms may also be involved, and can explain the value of VCR in the treatment of thrombocytopenic disorders.

Despite these interesting preclinical data, experience on the use of VCR in the treatment of acute-phase TTP patients is limited to anecdotal cases and the experience of the *TTP U.S. Medical Research Group*;[64,70] indeed, based on the encouraging results of a standardized regimen including exchange plasmapheresis, VCR and corticosteroids (8 of 9 TTP patients promptly responded to the treatment which included VCR at a dose of 1.4 mg/m^2 given i.v., on days 1, 4, 7 and 10), Gutterman proposed such a regimen as a reasonable initial treatment for TTP.[70]

At present, however, there are too few cases to conclude that VCR should be used as first line therapy in acute TTP; also, the high incidence of relapses in the U.S. series suggests more caution. The use of VCR may be considered in patients with refractory (see below) or recurrent TTP.

Is there a treatment for plasma-exchange-resistant patients?

As we have already seen, the use of plasma manipulation and especially of PE, alone or combined with drugs, has so dramatically improved the prognosis of TTP patients that the overall figure of complete responses currently exceeds 75%.

Nonetheless, even in the series with the highest survival rates, 10-15% of TTP patients fail to respond to treatment and die in spite of all efforts; such deaths are even less well tolerated considering that TTP strikes very early in life.

Some negative prognostic factors have been identified: both particularly severe neurologic damage when starting treatment and a low PE/days ratio – i.e., a low frequency of PE treatment – were statistically correlated with no response to PE,[71] which facts do not limit the urgent need of alternative treatment methods for this subgroup of patients.

No standardized treatment has yet been found for PE-resistant patients; indeed, the criterion of PE-resistance is ill-defined, since there is no consensus on when to stop – and resume – plasma therapy. Also, some authors suggested that the use of PE with cryosupernatant could overcome the resistance to PE.[24]

Splenectomy

Some reports have suggested the effectiveness of splenectomy in cases that do not respond to plasma therapy.[72-74] Splenectomy might theoretically be effective in that it removes a major site of synthesis of a supposedly pathogenetic antibody or of a vWF cofactor,[75] although some reported benefits attributed to splenectomy may actually result from the intraoperative administration of large amounts of plasma.

Furthermore, two small studies suggested the possibility of a detrimental effect of splenectomy in TTP;[43,76] in particular, a recent report showed a higher mortality rate and a longer disease duration in 13 TTP patients who had undergone splenectomy, compared with 39 patients continuing on plasma therapy.[76]

Finally, as correctly stressed by Ruggenenti and Remuzzi,[75] the results of delayed splenectomy would be biased by patient selection and would evade the early mortality of TTP.

Vincristine

Gutterman first showed the effectiveness of VCR as a rescue treatment in TTP cases refractory to plasma therapy. Interesting results were also recorded by the *Italian Co-operative Group* in plasma-exchange-resistant TTP patients.[77,78]

Indeed, 50% of successful treatment outcomes observed in the Italian study should be regarded as a positively good result in this subgroup of patients, whose prognosis is so bad due to both resistance to apheresis and their consequently severe status at the beginning of VCR treatment. In fact, VCR treatment failed in half the cases, but the patients who died had extremely severe neurologic and hematologic impairment at the time of the first VCR administration. In contrast, the remaining patients were cured with this drug, which clearly yielded a previously unobtained complete remission.[77]

Based on these observations, the same *Italian Cooperative Group for TTP* included VCR as salvage treatment within its national multicenter protocol aimed at evaluating the role of antiplatelet drugs in the acute phase of the disease; 9 patients who did not achieve a response after acute-phase treatment received VCR: 8 of them achieved a complete and lasting remission following such a salvage treatment.[44] Again, this stresses the high potential of VCR in the treatment of plasma-therapy-resistant TTP patients.

Other cytotoxic agents

Anecdotal cases of TTP patients who were refractory to plasma manipulation techniques and responded to immunosuppressant agents other than VCR have been reported in the literature. Both cyclophosphamide and azathioprine have been used with the rationale of inhibiting hypothetical autoimmune processes involved in disease recurrence.[79,80] There are too few cases at present to draw any conclusion on the real efficacy of these agents but it should be stressed that the response to azathioprine in a single TTP patient was associated with the disappearance of unusually large vWF multimers from the circulation.[80]

Recent experimental evidence supporting an autoimmune hypothesis for the pathogenesis of TTP will probably revive the experimental use of several immunosuppressants in the treatment of TTP patients, especially in those with relapsing or refractory disease.

Treatment of secondary forms of TTP

Pregnancy-associated TTP

Although several pregnancy-associated diseases – e.g., HELLP syndrome and pre-eclampsia – may present clinico-laboratory similarities to TTP, with a consequently difficult differential diagnosis, TTP may develop during pregnancy, usually at 23-24 weeks of gestation.

Despite limited experience, it also appears that the outcome of TTP developing during pregnancy has improved since plasma therapy was introduced, as shown by Weiner *et al*.[81] Thus, plasma-exchange should be considered the treatment of choice for pregnancy-associated TTP.

However, the main problem in the management of such a rare association is clearly the correct diagnosis of TTP. Idiopathic TTP must be differentiated from pre-eclampsia and the HELLP syndrome because delivery – the treatment of choice for the latter conditions – is usually not recommended as first line therapy to stop the course of TTP in pregnancy. Both Billio *et al*.[82] and Ruggenenti and Remuzzi.[75] provided valuable reviews on the problems of the differential diagnosis between TTP and these two other pregnancy-associated hematologic syndromes.

AIDS-related TTP

TTP has been increasingly reported as part of the complications of AIDS, with this association seen in as many as 30% of hospitalized TTP patients, at least according to some highly-biased case series.[83]

Again, management is the same as that routinely given to non-AIDS patients, that is plasma-exchange. However, immunosuppressants, especially steroids and cytotoxic agents, should be used with great caution since these drugs may increase the risk of opportunistic infections in already severely immunosuppressed patients.

Response to therapy appears to be different between HIV^+ TTP patients and overt AIDS patients with TTP, the latter having a very bad prognosis and responding poorly even to plasma manipulation techniques.[75]

Cancer and cancer-chemotherapy-related TTP

The occurrence of TTP in cancer patients has been well established.[84] Still, as far as the pathogenesis of cancer or chemotherapy-related TTP is concerned, the relative importance of the underlying neoplasm and of some of the chemotherapy agents these patients usually receive, especially mitomycin-C, has not yet been fully clarified.

In fact, since the patients receiving cancer chemotherapy drugs are being treated for malignancies, the relative contribution of the drugs or of the underlying cancer to TTP onset remains difficult to assess. Even though the endothelial-damaging properties of several chemotherapy agents are well known, the pro-aggregating activity of a number of tumors is also well documented, both in *in vitro* models and *in vivo.*[85,86]

Recent studies suggested that different mechanisms may be implicated in the pathogenesis of idiopathic and cancer/chemotherapy-related TTP cases. Nagaya *et al*. found that the levels of the cytokines tumor necrosis factor-α, interleukin-1 and interleukin-6, are increased in patients with *de novo* TTP/HUS and disseminated intravascular coagulation (DIC) but not in those with mitomycin-C-induced TTP/HUS, while vWF antigen and low molecular weight vWF multimers are decreased in *de novo* TTP/HUS but increased in DIC and in the drug-induced syndrome.[87] On the other hand we demonstrated that, in contrast to idiopathic TTP, cancer/chemotherapy-related TTP presents increased nitric oxide production.[88,89]

Another open question is whether TTP cases arising during circulating progenitor cell (CPC) transplantation procedures for solid tumors should be considered within the family of cancer chemotherapy-related TTP or should be regarded as a completely different entity, also in terms of required treatment options. Certainly, the use of submyeloablative doses of antiblastic drugs as CPC mobilizing agents seems to support the hypothesis of a primitive endothelial damage as the main pathogenetic factor for the development of TTP in these patients.

Notably, in cancer/chemotherapy-associated TTP patients, administration of blood products often results in exacerbation of the symptoms, so that common therapeutic procedures are less effective than in idiopathic TTP patients.

An effective procedure recently proposed to treat these patients is the perfusion of autologous plasma over filters containing staphylococcal protein A (PSA) covalently bound to polyacrylamide beads. This treatment can remove possibly pathogenetic circulating immunocomplexes from plasma and it proved to be highly effective in this particular subgroup of patients.[84,90,91] Overall, the results of PSA immunoad-

sorption seem to be better than those obtained with plasma-exchange, but only larger studies will eliminate any selection bias and definitely confirm or dismiss the above assumption.

Conclusions

At the dawn of the 21st century, several questions about TTP treatment and pathogenesis have been answered. Still, numerous important issues remain open and the quite satisfactory remission rates we can achieve today must be further improved. We need international co-operation between TTP study groups to set up multicenter trials on adequately large series of patients affected by this uncommon disease, so that in this new millenium TTP will be among the diseases which have been definitely defeated by man's clever mind and heart.

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All the three authors contributed equally to the paper.

Disclosures

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