Thrombotic thrombocytopenic purpura (TTP), or Moschkovitz’s disease, is an uncommon blood syndrome clinically characterized by a pentad of thrombocytopenia, microangiopathic Coombs’ negative anemia, fever, signs of neurologic involvement and renal symptoms.1

The relationship between the complex and proteiform clinical pattern of TTP and the thrombotic lesions of capillaries and arterioles, which Baehr et al. first demonstrated in 1936,2 has been reassessed of late. Nevertheless, the exact pathogenesis of TTP remains a partially unsolved enigma.

The enhanced platelet aggregation which occurs in TTP patients and is the major cause of both the above thrombi and consequent consumption thrombocytopenia, is probably due to an imbalance between unknown agents insulting endothelial wall and defense factors, such as prostacyclin (PGI2). Several reports suggested an aberration of PGI2 activity as a critical step in the pathogenesis of TTP. Therefore, PGI2 was proposed as an alternative treatment for TTP patients.

We report the results obtained with increasing doses (from 2 ng/Kg/min to 10 ng/Kg/min in 5 days) of PGI2 – as epoprostenol – in 4 TTP patients from the retrospective series of the Italian Cooperative Group who were considered resistant to conventional plasma-exchange (PE)-based treatments.

Despite PGI2 infusion, 2 patients died, while the extant 2 achieved stable complete remission. Notably, the only patient whose PE was administered with adequate frequency and for an adequate period of time, and thus the only unquestionably PE-resistant patient, was also resistant to PGI2 infusion. Major side-effects were few and observed at the highest doses.

In our experience and from the analysis of the literature, which, as far as we know, includes only 23 patients treated with PGI2-like substances, the role of PGI2 in the treatment of TTP appears to be modest. Maybe the identification of subgroups of TTP patients exhibiting some defects in PGI2 metabolism, together with the use of more manageable PGI2 analogs, such as iloprost, could revive interest in these molecules in the future.

Key words: TTP, Moschkovitz’s disease, resistant disease, PGI2, epoprostenol
such as prostacyclin (PGI₂), a strong natural inhibitor of platelet activation and aggregation. Several reports suggested an aberration of PGI₂ activity as a critical event in the pathogenesis of both TTP and hemolytic uremic syndrome (HUS), in terms of deficient PGI₂ synthesis or of accelerated PGI₂ degradation.

Because of such possibilities, PGI₂ (as epoprostenol) has been used, as i.v. infusion, to treat some TTP patients. However, since the number of epoprostenol-treated patients is limited and conflicting results were obtained, no definitive conclusions can be drawn on the actual effectiveness of the drug.

We report the results obtained with increasing doses of this drug, between 1984 and 1988, in 4 TTP patients from the retrospective series of cases of the Italian Cooperative Group for TTP (see Appendix).

**Patients and Methods**

All patients, 2 men and 2 women (median age: 26 years, range: 23-42), were diagnosed as having TTP in the presence of the following signs: thrombocytopenia (<100×10⁶/L), microangiopathic hemolytic anemia (demonstrated by the presence of schizocytes in peripheral blood smears and high LDH levels), no disseminated intravascular coagulation, no anti-erythrocyte and anti-platelet antibodies and, finally, signs of neurologic and renal involvement. Patients’ characteristics at diagnosis are summarized in Table 1. In two cases a bone marrow biopsy and in one case a gingival biopsy further confirmed the diagnosis of TTP, showing the pathognomonic hyaline, PAS-positive thrombi localized in the small arterioles and capillaries.

Before receiving epoprost enol, all patients failed to respond to plasma-exchange (PE) treatment. Attending physicians considered patients #1, #3 and #4 resistant to PE because none of them exhibited a significant and/or steady increase in platelet count, while their LDH levels remained high and severe clinical neurologic symptoms persisted (Figures #1, 2 and 4). In contrast, patient #2 exhibited laboratory signs of remission well before being started on PGI₂, but the rapid worsening of his neurologic symptoms suggested the, maybe premature, resort to a salvage treatment, which however turned out to be decisive (Figure #3).

Combined with PE, all patients received other drugs which had been demonstrated or were supposed to be active in TTP – i.e., corticosteroids alone in 1 patient and combined corticosteroids and anti-platelet drugs in another (Table 2). Two patients also received platelet concentrates, although their use in TTP is extremely controversial; indeed, platelet administration might yield material for fresh thrombi in the microcirculation. In fact, platelet count did not increase in the least, after platelet infusion, in patient #3 (Figure #4), who exhibited neither clinical nor neurologic worsening.

After the patients or their closest relatives had given their informed consent, all patients were treated with cycles of increasing doses of epoprostenol (2 ng/kg/min, as continuous i.v. infusion, on day 1, 4 ng/kg/min on day 2, 6

<table>
<thead>
<tr>
<th>#</th>
<th>Sex</th>
<th>Age</th>
<th>Fever</th>
<th>Hgb (g/dL)</th>
<th>Plt (mm³)</th>
<th>LDH (U/L)</th>
<th>CNS impairment</th>
<th>Renal impairment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>35</td>
<td>No</td>
<td>6.5</td>
<td>35,500</td>
<td>2,100</td>
<td>hemiparesis</td>
<td>No</td>
<td>Dead</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>42</td>
<td>Yes</td>
<td>9.3</td>
<td>30,000</td>
<td>1,177</td>
<td>aphasia</td>
<td>No</td>
<td>CR, alive</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>23</td>
<td>Yes</td>
<td>9.2</td>
<td>25,000</td>
<td>1,838</td>
<td>headache</td>
<td>Yes</td>
<td>CR, alive</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>24</td>
<td>Yes</td>
<td>6.4</td>
<td>23,500</td>
<td>2,500</td>
<td>aphasia</td>
<td>Yes</td>
<td>Dead</td>
</tr>
</tbody>
</table>
ng/kg/min on day 3, 8 ng/kg/min on day 4, and finally 10 ng/kg/min on day 5).

The following criteria were used to evaluate both complete and partial response to treatment: platelets > 150 $10^9$/L, reticulocytes < 100 $10^9$/L, LDH < 300 U/L, azotemia < 50 mg%, creatinine < 1.2 mg %, and haptoglobin > 40 mg % for complete remission, platelets < 100 $10^9$/L, and LDH < 300 U/L for partial remission.

Two other patients from the Italian Cooperative Group case series received PGI$_2$, but the frequency of PGI$_2$ infusion in these patients was extremely low (1 and 2 days, respectively); they subsequently received unsuccessful vincristine sulfate boluses as salvage treatment. Therefore, both patients were excluded from this survey.

### Results

Despite the administration of growing doses of PGI$_2$, 2 patients died of cerebral hemorrhage, few days after the completion of PGI$_2$ infusion, having shown no signs of improvement in clinical conditions and/or bio-humoral variables during treatment (Figures #1 and #2). In both cases the diagnosis of cerebral hemorrhage was confirmed at autopsy. An episode of mild bradycardia (50 beats/min, a 34 beats/min decrease from the pre-infusion heart rate) in one patient and marked hypotensive episodes in both patients (~30 mmHg, on the average), were observed at 8-10 ng/Kg/min PGI$_2$ doses. These side-effects were rapidly reversed by temporarily decreasing the infusion rate.

The remaining 2 patients achieved stable complete remission with PGI$_2$ infusion; platelet count started rising after 3 and 2 days of treatment, respectively, continued increasing after the end of the treatment, and reached the values consistent with the diagnosis of complete remission 15 and 6 days after the start of PGI$_2$ infusion (Figures #3 and 4).

Again, side-effects were recorded at 8 ng/kg/min doses and included headache, flushing, tachycardia (+15 beats/min, on the average) and hypotension (~20 mmHg, on the average) due to the vasodilator effect of the drug. Nevertheless, both patients could complete the scheduled treatment, with no need to modify the dosage of PGI$_2$.

No maintenance therapy was considered for the 2 patients who responded to PGI$_2$ treatment, and no relapses were observed; the patients are all under periodical follow-up, still alive and well and presenting no signs of disease activity.

### Discussion

As mentioned above, PGI$_2$ metabolism has been referred to the pathogenesis of TTP and HUS in terms of deficient synthesis or, on the contrary, of accelerated degradation. The hypothesis of deficient PGI$_2$ synthesis was proposed by Remuzzi et al., who reported on a
Figure 1. Unsuccessful PGI2 infusion in patient #1 after the failure of combined PE and methylprednisolone.

Figure 2. Unsuccessful PGI2 infusion in patient #4. This is the only one clearly resistant to standard treatment, having undergone PE sessions with an adequate frequency, and having also simultaneously received anti-platelet drugs and cortisone.
Figure 3. Patient #2 achieved complete remission after the failure of combined PE and platelet concentrates treatment. Even though this patient was showing biohumoral signs of remission before PG12 infusion, his neurologic status dramatically worsened under PE treatment.

Figure 4. Patient #3 achieved complete remission after PE and then platelet concentrates failed. Remarkably, after the infusion of platelet concentrates, platelet count did not improve, suggesting the possibility that exogenous platelets could feed the platelet destruction mechanism within peripheral microcirculation microthrombi.
family with HUS whose serum appeared to elicit a subnormal stimulation of PGI₂ production when incubated with rabbit aortic rings in vitro. Subsequent studies suggested that serum may contain a PGI₂-stimulating factor that, if deficient, may lead to compromised PGI₂ production, inadequate to face excessive platelet aggregation. However, the existence of a unique PGI₂-stimulating factor, which is probably missing in TTP and HUS patients, has never been unquestionably proved, while there are many factors (cytokines and activated neutrophils included) which can stimulate PGI₂ synthesis. It is therefore highly questionable whether in these diseases any specific PGI₂-stimulating factor is deficient or not.

Moreover, more recent data suggest the possibility that PGI₂ deficiency may be secondary, especially in HUS patients, to the toxic effect of bacterial toxins or chemical compounds (such as the antiblastic drug mitomycin-C) on the endothelial cell biosynthesis of PGI₂. Even though HUS cases are increasingly associated with Shiga-like toxin-producing Escherichia Coli strains, however, such an association is absent in TTP and quite anecdotic is also the association between TTP and the administration of compounds like mitomycin-C.

In regard to the hypothesis of accelerated PGI₂ degradation, Wu et al. demonstrated this phenomenon to be associated, in some TTP patients, with reduced PGI₂ binding activity in serum. As a result of these defects, PGI₂ plasmatic half-life is shortened in some TTP patients because of defective PGI₂ binding.

Moreover, defects in PGI₂ binding have also been reported recently in subjects affected with coronary artery disease, supporting the notion that PGI₂ binding plays a major role in regulating PGI₂ activity and in the pathogenesis of various microvascular thrombotic events.

In conclusion, PGI₂, which is a strong natural inhibitor of platelet activation and aggregation, acting at damaged vascular sites, has been referred to the pathogenesis of both TTP and HUS. In the case of TTP, some evidence supports the hypothesis of accelerated PGI₂ degradation, even though we are certainly far from any definitive conclusion on its actual implication. For all these reasons, epoprostenol has been considered a potentially useful agent to treat TTP, at least in the second instance, after the failure of PE, which is undoubtedly the treatment of choice for TTP.

As far as we know, only 17 TTP patients have been treated with epoprostenol, partly because of the rarity of this disease (and rarer still, therefore, are PE-resistant patients), and partly because of the poor manageability of this drug, which is unstable in aqueous solution and needs continuous infusion, besides exhibiting potent vasodilator effects.

Of 17 patients reported in the literature, 9 achieved complete and stable remission, while 3 achieved complete remission but rapidly relapsed, while no therapeutic effects of PGI₂ were observed in the extant 5 patients.

However, the presence must be stressed of a number of spurious TTP cases in this group of patients. An HIV-positive patient developed acquired type-II von Willebrand disease during TTP, while in another case TTP developed after allogeneic bone marrow transplantation for multiple myeloma, total body irradiation and high-dose chemotherapy having been considered the causes of diffuse endothelial damage resulting in the clinical pattern of TTP. Another patient had associated mixed connective tissue disease, and all of the 3 patients reported by Stein, despite achieving complete remission with PGI₂ infusion, subsequently relapsed with a clinical picture of immunogenic thrombocytopenic purpura (ITP).

A synthetic review of all the reported cases of prostacyclin-treated TTP patients can be found in Table 3.

Regarding our patients, little can be added to what can be inferred from the literature, both because our series included only 4 patients, and because of the results. The fact that 50% of our patients who were considered resistant to PE achieved complete remission by means of epoprostenol infusion might revive interest in this drug, and especially in iloprost, its recently developed and more stable analog.

As for the treated patients, if on the one hand none of them responded to PE, on the other hand the treatment had been administered with
poor frequency in patient #1 and discontinued too soon in patients #2 and 3. In a previous paper we demonstrated that the patients whose PE sessions are closer in time (PE/days ratio approaching 1), achieve complete remission more easily, in less time and with fewer sessions than the patients treated with lower frequency. Moreover, it has been postulated that no fewer than 10 PE sessions must be performed as close in time as technically feasible, to precisely assess possible PE efficacy.

Thus, patient #4 appears as the only one undoubtedly resistant to treatment, having undergone many PE sessions – with suboptimal but nonetheless adequate frequency – and having also simultaneously received anti-platelet drugs and cortisone. Therefore, the failure of epoprostenol treatment in this patient might be of greater value, suggesting the possible ineffectiveness of this treatment.

Nevertheless, whether the above new analog of PGI2, iloprost (which has been developed of late and is much more manageable than epoprostenol), will be useful in TTP patients, as it seems to be in patients with other vascular disorders and tissue injures, remains to be investigated.

The recent experience of Sacripanti et al., although seeming to support the possible efficacy of iloprost in thrombotic microangiopathies (both TTP and HUS), was probably vitiated by the combined administration of PE; in fact, in the absence of a control group, the extent of iloprost contribution to improving the efficacy of conventional PE cannot be assessed.

A major progress would be the identification of subgroups of TTP patients exhibiting some defect in PGI2 production or metabolism for whom this treatment could be preferentially attempted.

Table 3. Review of the published cases of PGI2-treated TTP patients

<table>
<thead>
<tr>
<th>#</th>
<th>Author (ref.)</th>
<th>Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hensby CN (6)</td>
<td>no response</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Budd GT (7)</td>
<td>no response</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>FitzGerald GA (8)</td>
<td>CR</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Rosove MH (9)</td>
<td>CR</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Johnson JE (10)</td>
<td>no response</td>
<td>—</td>
</tr>
<tr>
<td>6-8</td>
<td>Stein RS (11)</td>
<td>all 3 pts. had CR, then relapsed</td>
<td>all 3 pts. relapsed with a clinical picture characteristic of ITP</td>
</tr>
<tr>
<td>9</td>
<td>Trono D (12)</td>
<td>CR</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Durrant STS (13)</td>
<td>CR</td>
<td>PGI2 as Nafazatrom</td>
</tr>
<tr>
<td>11</td>
<td>Payton Cd. (14)</td>
<td>CR</td>
<td>no PE was administered</td>
</tr>
<tr>
<td>12, 13</td>
<td>Guelpa G (15)</td>
<td>CR, CR</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>Ter-Borg EJ (16)</td>
<td>no response</td>
<td>associated MCTD</td>
</tr>
<tr>
<td>15</td>
<td>Beris P (17)</td>
<td>CR</td>
<td>associated HIV infection and type-II von Willebrand disease</td>
</tr>
<tr>
<td>16</td>
<td>Tschuchnigg M (18)</td>
<td>no response</td>
<td>TTP developed after ABMT</td>
</tr>
<tr>
<td>17</td>
<td>Tardy B (19)</td>
<td>CR</td>
<td>—</td>
</tr>
<tr>
<td>18-23</td>
<td>Sagripanti (37)</td>
<td>all CRs</td>
<td>PGI2 as Iloprost together with PE</td>
</tr>
</tbody>
</table>

ITP: idiopathic thrombocytopenic purpura; MCTD: mixed connective tissue disease; ABMT: allogeneic bone marrow transplantation.
References

Appendix

Centers adhering to the Italian Cooperative Group for TTP

Divisione Ematologia, Ospedale Generale, Bolzano (O. Prinoth); Unità di Ematologia, Ospedale Santa Chiara, Trento (M. Rubertelli); Centro Trasfusionale, Ospedale Civile, Padova (G. Ongaro); Divisione Ematologia, Ospedale Civile, Vicenza (F. Rodeghiero); Divisione Nefrologia, Ospedale Niguarda, Milano (G. Busnach); Centro Trasfusionale, Ospedale Maggiore, Lodi (G. Cambiè); Divisione di Ematologia, I.R.C.C.S. Policlinico San Matteo, Pavia (A. Canevari); Ospedale Civile, S. Giovanni Rotondo (M. Carotenuto); Divisione Ematologia, Ospedale Pugliese, Catanzaro (G. Leda); Servizio Immunologia e Trasfusionale, Ospedali Riuniti, Sassari (G. Bertrand); Divisione Ematologia, Ospedale Businco, Cagliari (A. Broccia); Divisione Medicina V, Ospedale Regionale, Parma (M. Poli); Ospedale Serravalle, Palermo (A. Chimè); Servizio Trasfusionale, Policlinico Gemelli, Roma (G. Menichella); Servizio Immunologia e Trasfusionale, Ospedale Civile, Pescara (A. Iacone); Istituto di Ematologia L. & A. Seràgnoli, Università di Bologna (L. Gugliotta); Istituto Terapia Medica, I.R.C.C.S. Policlinico San Matteo, Università di Pavia (C. Porta); Istituto Clinica Medica II, I.R.C.C.S. Policlinico San Matteo, Università di Pavia (E. Ascarì, National Coordinator); Servizio Immunologia e Trasfusionale, I.R.C.C.S. Policlinico San Matteo, Pavia (L. Salvaneschi); Centro Trasfusionale, Ospedale di Careggi, Firenze (G. Avanzi); Servizio Immunologia e Trasfusionale, Ospedale Santa Chiara, Pisa (P. Fosella); Divisione di Ematologia, Ospedale S. Camillo, Roma (N. Petti); Divisione di Medicina, Ospedale Civile, Varallo Sesia (L. Anselmetti); Sezione di Ematologia, Università di Roma (G. Isacchi); Istituto 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 Medicina II, Ospedali Riuniti, Bergamo (M. Gorini); Divisione Medicina B, Ospedale Civile, Biella (M. Antonini); Ambulatorio Oncologia-Ematologia, Ospedale Civile, Aosta (F. Salvi); Servizio Trasfusionale, Ospedale Galliera, Genova (R. Adamì); Divisione Ematologia, Policlinico, Modena (U. Di Prisco); I Divisione Medicina Generale, Arcispedale S. Maria Nuova, Reggio Emilia (L. Masini); Divisione Medicina Generale, Ospedale Maggiore, Crema (E. Bobbio-Pallavicini, Group Responsible).