

Efficacy and Safety Profile of Solvent/Detergent Plasma in the Treatment of Acute Thrombotic Thrombocytopenic Purpura: A Single-Center Experience

Elvira Edel^a Haifa Kathrin Al-Ali^b Susanne Seeger^c Dörte Kauschat^d Gert Matthes^a

^a Institute of Transfusion Medicine,

^b Department of Hematology and Oncology, University Hospital Leipzig,

^c Octapharma GmbH,

^d Octapharma GmbH, Germany (present address Sanofi-Aventis)

Key Words

Thrombotic thrombocytopenic purpura · TTP ·
Therapeutic plasma exchange · TPE ·
Solvent/detergent-treated plasma · SDP · ADAMTS-13

Summary

Background: Thrombotic thrombocytopenic purpura (TTP) is a rare clinical disorder which was associated with poor prognosis for a long time. The outcome has been improved by the consistent introduction of therapeutic plasma exchange (TPE) as standard treatment of TTP. **Patients and Methods:** We describe our experience in the use of solvent/detergent-treated plasma (SDP) for TPE in TTP. We retrospectively analyzed acute TTP episodes in 8 patients (mean age = 27 years, range 18–44 years) treated with TPE using SDP with regard to tolerability and efficacy. **Results:** All 8 patients were positive for anti-ADAMTS-13 antibody. Seven out of 8 had a severe ADAMTS-13 deficiency. All patients responded rapidly to SDP TPE with an increase in platelet count to above $150 \times 10^9/l$. Hemolytic anemia disappeared over the treatment period. Approximately 2,000 l SDP were used for more than 500 treatments. Treatment with SDP was well tolerated; none of the patients experienced an adverse drug reaction after exposure to SDP. No major complications occurred even after multiple TPE. **Conclusion:** Our investigations suggest that TPE using SDP as replacement fluid is an effective treatment for TTP. The data described also indicate that SDP might offer the benefit of reducing adverse drug reactions.

Schlüsselwörter

Thrombotisch-thrombozytopenische Purpura · TTP ·
Therapeutischer Plasmaaustausch · TPE ·
Solvent/Detergent-behandeltes Plasma · SDP · ADAMTS-13

Zusammenfassung

Hintergrund: Die thrombotisch-thrombozytopenische Purpura (TTP) ist eine seltene Erkrankung, die für die Patienten lange mit einer ungünstigen Prognose verbunden war. Die Überlebensrate konnte erst durch eine konsequente Einführung des therapeutischen Plasmaaustauschs (TPA) als Standardtherapie der TTP verbessert werden. **Patienten und Methoden:** Wir beschreiben unsere Erfahrungen mit dem Einsatz von Solvent/Detergent-behandeltem Plasma (SDP) in der TPA zur Behandlung der TTP. Akute TTP-Episoden von 8 Patienten (Durchschnittsalter 27 Jahre, Bereich 18–44 Jahre) wurden im Hinblick auf die Verträglichkeit und die Wirksamkeit des verwendeten Plasmas retrospektiv untersucht. **Ergebnisse:** Alle 8 Patienten wurden positiv auf Anti-ADAMTS-13-Antikörper getestet. Sieben der 8 Patienten wiesen eine schwerwiegende ADAMTS-13-Defizienz auf. Alle Patienten reagierten auf die TPA mit einem schnellen Anstieg der Thrombozyten auf $150 \times 10^9/l$. Die hämolytische Anämie bildete sich im Verlauf der Behandlung zurück. Es wurden mehr als 500 Behandlungen durchgeführt und annähernd 2000 l SDP eingesetzt. Die Behandlungen mit SDP wurden sehr gut vertragen. Keiner der Patienten entwickelte eine allergische Reaktion nach Gabe von SDP. Auch nach mehrfacher TPA traten keine schwerwiegenden Komplikationen auf. **Schlussfolgerung:** Unsere Erfahrungen zeigen, dass der TPA mit SDP eine effektive Behandlung der TTP ist. Die erhobenen Daten weisen zudem darauf hin, dass SDP zu einer Reduktion von Nebenwirkungen führen kann.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disseminated thrombotic microangiopathy first described by Moschcowitz in 1924 [1]. TTP is characterized by acute thrombocytopenia, microangiopathic hemolytic anemia and neurological abnormalities with no clinically apparent alternative explanation for thrombocytopenia and hemolysis [2]. Additional clinical signs supporting the diagnosis are impaired renal function and fever [3].

Different causes and mechanisms are involved in the pathogenesis of TTP. The common feature is the presence of ultralarge von Willebrand factor (UL-vWF) multimers in the plasma of TTP patients [4]. Upon synthesis of vWF by endothelial cells and secretion into the circulation, vWF is normally cleaved by vWF-cleaving-protease ADAMTS-13, a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13 [5, 6]. Acquired as well as congenital TTP is often associated with severe deficiency of ADAMTS-13 [7]. Deficiency of ADAMTS-13 results in the accumulation of UL-vWF multimers and leads to the development of vWF-platelet aggregation and intravascular thrombosis, one of the characteristics of TTP. In some cases of acquired TTP, ADAMTS-13 deficiency has been associated with the presence of inhibitory antibodies [8, 9].

The incidence of TTP in the general population appears to be approximately 3.8 per million [10, 11]. Until the introduction of plasma therapy, including therapeutic plasma exchange (TPE) and/or plasma infusion, acute TTP was almost always fatal. However, TPE is now widely used as standard treatment allowing about 80–90% of treated patients to survive an episode of TTP [12, 13]. Although representing a significant improvement in TTP therapy, TPE is associated with complications related to the procedure itself, catheter-related complications and adverse reactions dependent on the plasma product used [14–16].

The choice of replacement fluid appears to be one of the crucial factors and is still a controversial issue [2, 17]. In common use are cryosupernatant (CPP) and fresh frozen plasma (FFP), but recently solvent/detergent-treated plasma (SDP) has increasingly been used [2, 18–23]. The occurrence of plasma-related allergic reactions due to the use of CPP and FFP are reported [23, 24]. However, recent studies indicated a reduced risk of complications if SDP was used, even in patients who developed allergic reactions after the use of FFP [19–21].

In recent years transfusion-related acute lung injury (TRALI) has been recognized as an important adverse reaction of blood products [25, 26]. In the UK and USA it is the most significant cause of transfusion-related mortality and morbidity [26, 27]. In Norway however, where only SDP is used, TRALI has not been reported as an adverse event [28].

We therefore used SDP as replacement fluid in TPE in order to verify its effectiveness in the treatment of TTP and its beneficial effect in reducing the number of allergic reactions and adverse events [29, 30].

Patients and Methods

Medical charts and the plasmapheresis unit records of all patients diagnosed with acute TTP were reviewed retrospectively. The patients had been treated with TPE between 1998 and 2006 at the Institute of Transfusion Medicine at the University Hospital Leipzig, Germany.

TTP was diagnosed when the patient presented with thrombocytopenia (platelet count $<150 \times 10^9/l$) and microangiopathic hemolytic anemia (schistocytosis; fragmentation of red blood cells) with or without renal dysfunction, neurological abnormalities or fever. All patients have received RBCs due to their medical condition before the diagnosis TTP was made. The patient characteristics and initial laboratory data are shown in table 1. TPE was performed until a platelet count above $150 \times 10^9/l$, stable hemoglobin (>7.5 mmol/l) and creatinine concentration (<84 $\mu\text{mol/l}$) and LDH results between 2.25–5.35 $\mu\text{kat/l}$ (37°C) were maintained. Relapse was defined as recurrence of thrombocytopenia (platelet count $<150 \times 10^9/l$), return of schistocytes in the peripheral blood, and reduced ADAMTS-13 activity ($<5\%$) with or without antibodies against ADAMTS-13. Concomitant medications were used according to physician's discretion following the recommendation of the German Society for Hematology and Oncology (Deutsche Gesellschaft für Hämatologie und Onkologie) and the international guideline [2]. The information about the concomitant medications received is provided in detail in the case report section. The assays of ADAMTS-13 activity and ADAMTS-13 antibodies were performed as previously described [31].

Therapeutic Plasma Exchange

TPE was performed with the COBE Spectra Apheresis System (CaridianBCT INC., Lakewood, CO, USA). The system separates the plasma from cellular blood components by centrifugal technology. TPE was started immediately after diagnosis of TTP using SDP (Octaplas[®], Octapharma GmbH, Langenfeld, Germany) as replacement fluid. The volume of plasma removed during a plasma exchange was 1–1.5 plasma volumes. The patients were treated daily with TPE until stable remission was achieved, after which the frequency of TPE was reduced slowly to taper the treatment. The patients were followed up to assess the durability of their response.

Results

Case Reports

Patient 1

TTP was diagnosed in a 30-year-old female patient with hematomas, excessive bleeding after tooth extraction and mental confusion. She showed a low platelet count ($11 \times 10^9/l$) and hemolytic anemia (1.5% schistocytosis). The ADAMTS-13 activity was below 3%, and anti-ADAMTS-13 antibodies were detected in her serum. She completed 23 TPEs with 140 l SDP in total (mean 6.1 ± 1.3 l/TPE; 81.33 ml/kg body weight (BW)) and was additionally treated with glucocorticoids. SDP was well tolerated without any adverse drug reaction. She was discharged from hospital without any further treatment and has been in remission for 5 years.

Patient 2

A 29-year-old male patient with a history of macrohematuria had thrombocytopenia ($28 \times 10^9/l$), schistocytosis (7.3%) and

Table 1. Patient characteristics and initial laboratory data

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, years / sex	30/female	29/male	20/female	44/male	21/male	28/male	18/female	24/female
Hemoglobin ^a , mmol/l	2.8	4.5	6.3	5.8	5.3	5	4.3	4.7
Platelet ^b × 10 ⁹ /l	11	28	14	48	11	15	23	5
LDH ^c , µkat/l	38.9	27.8	17.7	40.9	20.2	55.5	14.4	30.9
Creatinine ^d , µmol/l	110	177	95	244	87	226	69	253
RBC fragmentation, %	1.5	7.3	3.3	4.3	4	20	4.2	15
VWF-CP, %	3	4	<1	<1	3	<3	12	<2.5
Protease antibody	positive	positive	positive	positive	positive	positive	positive	positive
Symptoms	hematoma, bleeding after tooth extraction, somnolence, confusion	unconscious convulsion, macrohematuria	macrohematuria	hematoma, visual field defect	macrohematuria, petechia	hematoma, icterus, anemia	hematoma, vaginal bleeding gestation	renal insufficiency, unconsciousness, fetal death

RBC = Red blood cells; VWF-CP = von Willebrand factor-cleaving protease.

^aNormal laboratory value for hemoglobin 7.5–9.9 mmol/l.

^bNormal laboratory value for platelets 150–380 × 10⁹/l.

^cNormal laboratory value for creatinine 50–110 µmol/l.

^dNormal laboratory value for LDH 2.25–3.55 µkat/l; 37 °C.

an increased creatinine level of 177 µmol/l. The ADAMTS-13 activity was 4%, and anti-ADAMTS-13 antibodies were detected in his serum. TTP was diagnosed, and he received 48 TPEs overall with a total of 223 l SDP (mean 4.9 ± 0.6 l/TPE; 36.47 ml/kg BW) without any adverse drug reaction. He also received glucocorticoids to prevent further relapses. The patient was still in complete remission after 31 months.

Patient 3

A 20-year-old female patient with a history of macrohematuria was admitted to hospital with a low platelet count (15 × 10⁹/l) and schistocytes (3.3%). The ADAMTS-13 activity was below 1%, and anti-ADAMTS-13 antibodies were detected in her plasma; so TTP was diagnosed. A total of 63 TPEs with 206 l of SDP (mean 3.3 ± 0.9 l/TPE; 44.79 ml/kg BW) were well tolerated without adverse drug reaction. She was additionally treated with rituximab, glucocorticoids, heparin and immunoglobulin. She had a total of two relapses, but 1 year after diagnosis her ADAMTS-13 activity had normalized and no anti-ADAMTS-13 antibodies were detectable in the peripheral blood. She has been in complete remission for approximately 4 years.

Patient 4

A 44-year-old male patient presented with a history of chronic renal insufficiency, arterial hypertension and multiple cerebral infarcts. He was positive for anti-*Escherichia coli*-0157 antibodies. TTP was diagnosed on the basis of thrombocytopenia (platelet count 48 × 10⁹/l), increased creatinine level (244 µmol/l) and schistocytosis (4.3%). The activity of ADAMTS-13 was below 1%, and anti-ADAMTS-13 antibodies were detected in his plasma. Over 2.8 years he received a total of 122 TPEs with a mean volume of 4.5 ± 1.3 l SDP per TPE (43.20 ml/kg BW) without adverse drug reaction. During the course of the therapy he had five relapses, but he recovered quickly when daily TPE was recommenced. He was additionally treated with rituximab, glucocorticoids, heparin, aspirin and defibrotide. The patient has been in remission for the last 3 years.

Patient 5

A 21-year-old male patient presented with a history of macrohematuria and petechia. The diagnosis of TTP was made because of his low platelet count (11 × 10⁹/l) and the presence of schistocytes in his peripheral blood smear (4%). The ADAMTS-13 activity was reduced to 3%, and anti-ADAMTS-13 antibodies were detectable. His creatinine level was normal. Schistocytes decreased to 0.7% during the treatment period, and ADAMTS-13 activity normalized after 4 months of treatment with a total of 40 TPEs using 198 l SDP (mean 4.9 ± 0.4 l/TPE; 44.11 ml/kg BW). SDP was well tolerated without any adverse drug reaction. After discharge from hospital he received TPE a few times as an ambulant patient and short-term treatment with heparin to support TPE. The patient is still in complete remission after 2 years.

Patient 6

A 28-year-old male patient was admitted to hospital without distinct clinical symptoms. The diagnosis of TTP was made on the basis of thrombocytopenia (platelet count $15 \times 10^9/l$), anemia (Hb 5 mmol/l) and creatinine elevation (226 $\mu\text{mol/l}$). Additionally ADAMTS-13 activity was reduced (<3%), anti-ADAMTS-13 antibodies were detected in his serum, and schistocytes were present in a peripheral blood smear (20%). Overall, 51 TPEs using a total of 181 l SDP (mean 3.6 ± 0.6 l/TPE; 42.36 ml/kg BW) were administered and well tolerated by the patient without any adverse drug reaction. Supplementary medication included glucocorticoids, defibrotide and rituximab. The patient is still in complete remission after nearly 1 year.

Patient 7

An 18-year-old female in the 18th week of pregnancy presented with serious vaginal bleeding, anemia (Hb 4.3 mmol/l) and thrombocytopenia (platelet count $23 \times 10^9/l$). The diagnosis of TTP was made on the basis of her low platelet count ($23 \times 10^9/l$) and the presence of schistocytes in her peripheral blood smear (4.2%). The ADAMTS-13 activity was not reduced (12%), but anti-ADAMTS-13 antibodies were detected in her serum. A total of 36 TPEs with 116 l SDP (mean 3.2 ± 0.6 l/TPE; 38.92 ml/kg BW) were administered and well tolerated without any adverse drug reaction. Ultrasound diagnostics showed a normal course of pregnancy. No thromboembolic complications occurred. She completed her pregnancy successfully, and 16 months after her delivery was still in complete remission (platelet count $368 \times 10^9/l$).

Patient 8

A 24-year-old female in the 23rd week of pregnancy was admitted to hospital with loss of consciousness, renal insufficiency and anemia (Hb 4.7 mmol/l). Firstly the pregnancy was terminated because of fetal death. This event was not related to TTP but was the result of a true knot of the umbilical cord. The diagnosis of TTP was made because of thrombocytopenia (platelet count $5 \times 10^9/l$), increased creatinine level (253 $\mu\text{mol/l}$) and schistocytes (15%). The ADAMTS-13 activity was reduced (<2.5%), and anti-ADAMTS-13 antibodies were detected in her serum. Immediately after diagnosis she received TPE, and 4 weeks after therapy she regained consciousness and achieved complete remission. After discharge from hospital she received glucocorticoids. Two months later she suffered a relapse. After an interval of 2 months a second relapse occurred. In both cases she was treated with TPE and received glucocorticoids, defibrotide and rituximab. A total of 123 TPEs with 391 l SDP (mean 3.2 ± 0.4 l/TPE; 53 ml/kg BW) were administered and were well tolerated without any adverse drug reaction. She has had no additional episodes of TTP for 1.5 years.

Discussion

The standard treatment for acute TTP is daily TPE [2]. Plasma replenishes the missing ADAMTS-13, and the procedure allows large volumes to be given and assists in the removal of associated antibodies to ADAMTS-13 in those patients that have antibody-mediated disease. Although TPE is undoubtedly efficacious, the choice of replacement fluid is still under discussion.

FFP and CPP appear to be equally effective in the therapy of TTP [32–34]. Pooled SDP represents an alternative to single-donor FFP and CPP. Several studies have shown that SDP is less variable in composition and has more consistent levels of ADAMTS-13 activity and antigen than CPP and FFP where each unit is derived from one donor. The levels of ADAMTS-13 activity and antigen found in Octaplas were comparable to the average levels found in single-donor FFP. Consequently, infusion of SDP can replace the missing or neutralized ADAMTS-13 activity in TTP patients [35–37]. A number of studies and case reports confirm the efficacy of SDP in the treatment of TTP [19–21, 23, 38, 39]. In the report by Harrison et al. [19], one patient with acute TTP refractory to TPE with FFP and CPP achieved remission with SDP.

With TPE established as standard therapy, recently published studies have evaluated the risks/adverse events of this treatment. Rizvi et al. [16] categorized two groups of TPE complications: catheter-related and plasma-related adverse events. Whereas catheter-related adverse events are independent of the solution used for replacement, the number of plasma-related adverse events may be influenced by the choice of fluid.

The most common plasmatic adverse events are allergic reactions. Stanworth et al. [40] reported that allergic reactions to FFP are relatively common, with a frequency of around 1–3% of all transfusions. In countries where only SDP is used, fewer transfusion-associated allergic and anaphylactic reactions are reported [41, 42]. The Austrian hemovigilance data for 2003–2006 [42–45] showed a risk of allergic reactions of 0.053%/bag for FFP and 0.003%/bag for SDP. The risk of allergic reactions increases with the number of bags used. Therefore, the tolerability of the replacement fluid is of high importance for TTP patients.

A review of the literature shows that several TTP studies have considered the tolerability of different exchange fluids [46]. Reutter et al. [24] reported that two thirds of TTP patients developed allergic reactions during TPE therapy whether treated with FFP or CPP. Scully et al. [23] observed that allergic/urticarial and citrate reactions were more common with CPP (9.3%) than with SDP (3.1%) and that the difference was significant. McCarthy [21] reported that the use of SDP virtually eliminates allergic reactions. Some case reports suggest a reduction in allergic reactions in TTP patients after changing from FFP to SDP [20, 22]. Evans et al. [38] reported the well tolerated SDP treatment of 3 TTP patients,

Table 2. TPE treatment and closing laboratory data

Patient	Number of treatments	Total volume, l	Duration of treatment, months	Average volume per TPE, l	Mean volume exchanged/TPE, ml/kg BW	Post treatment values		
						Platelets ^a , × 10 ⁹ /l	LDH ^b , µkat/l	Creatinine ^c , µmol/l
1	23	140	1	6.10	81.33	183	4.94	85
2	48	223	4	4.85	36.47	239	3.50	66
3	63	206	13	3.27	44.79	413	4.58	49
4	122	544	34	4.45	43.20	136	3.26	135
5	40	198	4	4.94	44.11	343	2.92	66
6	51	181	5	3.55	42.26	159	2.81	94
7	36	116	3	3.23	38.92	267	3.01	49
8	123	391	7	3.18	53.00	402	2.73	55
Median	50	202	4.5	4.00	43.66	253	3.14	66

BW = Body weight.

^aNormal laboratory value for platelets 150–380 × 10⁹/l.

^bNormal laboratory value for creatinine 50–110 µmol/l.

^cNormal laboratory value for LDH 2.25–3.55 µkat/l; 37 °C.

without febrile or other adverse reactions. This may be a consequence of the purity of SDP which is free from cells and cellular debris, since plasma purity reduces the risk of adverse reactions [47–49].

Yarranton et al. [50] have reviewed the occurrence of venous thromboembolism (VTE) in 68 consecutive patients with TTP. Eight VTE events were identified in 7 female patients during TPE therapy. Octaplas was the last plasma to be used in TPE prior to the VTE in 7 out of 8 events although only 3 had received Octaplas exclusively. Octaplas is known to have reduced protein S activity. Theoretically, this may contribute to an increased risk of VTE when large volumes are transfused, but it was acknowledged by the authors that VTE is a multifactorial disease and several known precipitating factors for VTE were undoubtedly present in all cases reported. Recently, the same group published their positive experience with usage of Octaplas in 50 acute TTP episodes (alone or together with CPP) [23]. There were no reports of thrombotic events after TPE with Octaplas and fewer allergic reactions. Today they use Octaplas as first-line therapy for acute TTP episodes according to the recommendation of the national health department (UK, January 31, 2006).

Regarding viral safety, the use of SDP ensures maximum safety with respect to the risk of transmission of lipid-enveloped viruses because solvent/detergent treatment inactivates lipid-enveloped viruses, including recently detected and potential unknown viruses [51–54]. A combination of additional screening and the presence of neutralizing antibodies in the plasma pool results in a product that is safer with respect to the non-enveloped viruses B19 and HAV [52].

Furthermore FFP is commonly implicated in TRALI, a life-threatening complication of transfusion. Recently, a patient with TTP developed TRALI after TPE with FFP [55]. Most such events are caused by donor leukocyte-reactive anti-

bodies [56]. SDP does not contain detectable levels of leukocyte-reactive antibodies, possibly due to the at least 500-fold dilution of individual donations [57].

We have retrospectively analyzed the efficacy and tolerability of the treatment of 8 patients with acute TTP using SDP (Octaplas) as replacement fluid. Seven of the 8 patients had a severe deficiency in the vWF-cleaving protease ADAMTS-13, and all 8 patients were positive for inhibitory ADAMTS-13 antibodies. These patients required TPE at least as frequently as every second day.

The 8 patients underwent 50 TPEs/patient (median) with an average of 202 l SDP used overall (table 2). The mean volume of SDP/TPE was 4.20 ± 1.06 l. All patients responded to TPE with an increase in platelet count to more than 150 × 10⁹/l (table 2). Hemolytic anemia disappeared during the treatment. ADAMTS-13 inhibitory antibodies were partially or completely removed by TPE. A total of 506 treatments were carried out and 1,999 l plasma were used. None of the patients had an adverse drug reaction or a thrombotic event during exposure to SDP. No major complications occurred even after multiple TPE.

Our experience supports the data from published studies and demonstrates that the use of SDP for TTP is effective and tolerable.

However, it seems to be reasonable to confirm these promising safety results by exchanging clinical experience with SDP in the treatment of TTP on a more standardized basis.

Disclosure

E. Edel, H.K. Al-Ali and G. Matthes declared no conflict of interest. S. Seeger is employee of Octapharma GmbH. D. Kauschat is now employee of Sanofi-Aventis.

References

- 1 Moschcowitz E: Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. *Proc N Y Soc* 2006;24:21–24.
- 2 Allford SL, Hunt BJ, Rose P, Machin SJ: Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol* 2003;120:556–573.
- 3 Rock G, Kelton JG, Shumak KH, Buskard NA, Sutton DM, Benny WB: Laboratory abnormalities in thrombotic thrombocytopenic purpura. Canadian Apheresis Group. *Br J Haematol* 1998;103:1031–1036.
- 4 Moake JL, Byrnes JJ, Troll JH, Rudy CK, Hong SL, Weinstein MJ, Colanino NM: Effects of fresh-frozen plasma and its cryosupernatant fraction on von Willebrand factor multimeric forms in chronic relapsing thrombotic thrombocytopenic purpura. *Blood* 1985;65:1232–1236.
- 5 Dong JF, Moake JL, Nolasco L, Bernardo A, Arce-neaux W, Shrimpton CN, Schade AJ, McIntire LV, Fujikawa K, Lopez JA: ADAMTS-13 rapidly cleaves newly secreted ultralarge von Willebrand factor multimers on the endothelial surface under flowing conditions. *Blood* 2002;100:4033–4039.
- 6 Handin RI, Wagner DD: Molecular and cellular biology of von Willebrand factor. *Prog Hemost Thromb* 1989;9:233–259.
- 7 Tsai HM, Lian EC: Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med* 1998;339:1585–1594.
- 8 Furlan M, Robles R, Solenthaler M, Lammler B: Acquired deficiency of von Willebrand factor-cleaving protease in a patient with thrombotic thrombocytopenic purpura. *Blood* 1998;91:2839–2846.
- 9 Tsai HM, Li A, Rock G: Inhibitors of von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura. *Clin Lab* 2001;47:387–392.
- 10 Torok TJ, Holman RC, Chorba TL: Increasing mortality from thrombotic thrombocytopenic purpura in the United States – analysis of national mortality data, 1968–1991. *Am J Hematol* 1995;50:84–90.
- 11 Miller DP, Kaye JA, Shea K, Ziyadeh N, Cali C, Black C, Walker AM: Incidence of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. *Epidemiology* 2004;15:208–215.
- 12 Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, Spasoff RA: Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med* 1991;325:393–397.
- 13 Fontana S, Kremer Hovinga JA, Lammler B, Mansouri TB: Treatment of thrombotic thrombocytopenic purpura. *Vox Sang* 2006;90:245–254.
- 14 Mokrzycki MH, Kaplan AA: Therapeutic plasma exchange: complications and management. *Am J Kidney Dis* 1994;23:817–827.
- 15 Zeitler H, Ulrich-Merzenich G, Walger P, Bartels M, Goldmann G, Vetter H, Oldenburg J: Treatment of adults with clinically suspected severe thrombotic thrombocytopenic purpura – experiences of a single centre. *Transfus Med Hemother* 2007;34:64–72.
- 16 Rizvi MA, Vesely SK, George JN, Chandler L, Duvall D, Smith JW, Gilcher RO: Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic-uremic syndrome. *Transfusion* 2000;40:896–901.
- 17 Muncunill J: Thrombotic thrombocytopenic purpura (TTP): is any plasma useful to treat the TTP? *ISBT Science Series* 2007;2:233–239.
- 18 Moake J, Chintagumpala M, Turner N, McPherson P, Nolasco L, Steuber C, Santiago BP, Horowitz M, Pehta J: Solvent/detergent-treated plasma suppresses shear-induced platelet aggregation and prevents episodes of thrombotic thrombocytopenic purpura. *Blood* 1994;84:490–497.
- 19 Harrison CN, Lawrie AS, Iqbal A, Hunter A, Machin SJ: Plasma exchange with solvent/detergent-treated plasma of resistant thrombotic thrombocytopenic purpura. *Br J Haematol* 1996;94:756–758.
- 20 Kentouche K, Budde U, Furlan M, Scharfe V, Schneppenheim R, Zintl F: Remission of thrombotic thrombocytopenic purpura in a patient with compound heterozygous deficiency of von Willebrand factor-cleaving protease by infusion of solvent/detergent plasma. *Acta Paediatr* 2002;91:1056–1059.
- 21 McCarthy LJ, Dlott JS, Orazi A, Waxman D, Miraglia CC, Danielson CF: Thrombotic thrombocytopenic purpura: yesterday, today, tomorrow. *Ther Apher Dial* 2004;8:80–86.
- 22 Edel E, Matthes G: Treatment of thrombotic thrombocytopenic purpura (TTP) by plasma exchange. *Platelets* 2004;15:479–517.
- 23 Scully M, Longair I, Flynn M, Berryman J, Machin SJ: Cryosupernatant and solvent detergent fresh-frozen plasma (Octaplas) usage at a single centre in acute thrombotic thrombocytopenic purpura. *Vox Sang* 2007;93:154–158.
- 24 Reutter JC, Sanders KF, Brecher ME, Jones HG, Bandarenko N: Incidence of allergic reactions with fresh frozen plasma or cryo-supernatant plasma in the treatment of thrombotic thrombocytopenic purpura. *J Clin Apher* 2001;16:134–138.
- 25 Bux J: Transfusion-related acute lung injury (TRALI): a serious adverse event of blood transfusion. *Vox Sang* 2005;89:1–10.
- 26 Silliman CC, Ambruso DR, Boshkov LK: Transfusion-related acute lung injury (TRALI). *Blood* 2005;105:2266–2273.
- 27 Stainsby D, Jones H, Milkins C, Gibson B, Norfolk DR, Revill J, Atterbury CLJ: SHOT – Serious hazards of transfusion. Annual Report 2003. www.shotuk.org/.
- 28 Flesland O, Seghatchian J, Solheim BG: The Norwegian Plasma Fractionation Project – a 12 year clinical and economic success story. *Transfus Apher Sci* 2003;28:93–100.
- 29 Moake J, Chintagumpala M, Turner N, McPherson P, Nolasco L, Steuber C, Santiago-Borrero P, Horowitz M, Pehta J: Solvent/detergent-treated plasma suppresses shear-induced platelet aggregation and prevents episodes of thrombotic thrombocytopenic purpura. *Blood* 1994;84:490–497.
- 30 Harrison CN, Lawrie AS, Iqbal A, Hunter A, Machin SJ: Plasma exchange with solvent/detergent-treated plasma of resistant thrombotic thrombocytopenic purpura. *Br J Haematol* 1996;94:756–758.
- 31 Schneppenheim R, Budde U, Oyen F, Angerhaus D, Aumann V, Drewke E, Hassenpflug WA, Harberle J, Kentouche K, Kohne E, Kurnik K, Mueller-Wiefel DE, Obser T, Santer R, Sykora K-W: Von Willebrand factor cleaving protease and ADAMTS13 mutations in childhood TTP. *Blood* 2003;101:1845–1850.
- 32 Zeigler ZR, Shaddock RK, Gryn JF, Rintels PB, George JN, Besa EC, Bodensteiner D, Silver B, Kramer RE: Cryoprecipitate poor plasma does not improve early response in primary adult thrombotic thrombocytopenic purpura (TTP). *J Clin Apher* 2001;16:19–22.
- 33 Altuntas F, Aydogdu I, Kabukcu S, Kocyigit I, Cikim K, Sari I, Erkut MA, Eser B, Ozturk A, Kaya E, Cetin M, Keskin A, Unal A: Therapeutic plasma exchange for the treatment of thrombotic thrombocytopenic purpura: a retrospective multicenter study. *Transfus Apher Sci* 2007;36:57–67.
- 34 Rock G, Anderson D, Clark W, LeBlond P, Palmer D, Sternbach M, Sutton D, Wells G: Does cryosupernatant plasma improve outcome in thrombotic thrombocytopenic purpura? No answer yet. *Br J Haematol* 2005;129:79–86.
- 35 Heger A, Kannicht C, Römisch J, Svae TE: Normal levels of ADAMTS 13 and factor H are present in the pharmaceutically licensed plasma for transfusion (Octaplas) and in the universally applicable plasma (Uniplas) in development. *Vox Sang* 2007;92:206–212.
- 36 Yarranton H, Lawrie AS, Purdy G, Mackie IJ, Machin SJ: Comparison of von Willebrand factor antigen, von Willebrand factor-cleaving protease and protein S in blood components used for treatment of thrombotic thrombocytopenic purpura. *Transfus Med* 2004;14:39–44.
- 37 Rock G, Yousef H, Neurath D, Lu M: ADAMTS-13 levels in fresh, stored, and solvent detergent treated plasma. *Transfus Apher Sci* 2006;35:235–238.
- 38 Evans G, Llewelyn C, Luddington R, Baglin TP, Williamson LM: Solvent/detergent fresh frozen plasma as primary treatment of acute thrombotic thrombocytopenic purpura. *Clin Lab Haematol* 1999;21:119–123.
- 39 Allford SL, Harrison P, Lawrie A, Mackie IJ, Machin SJ: The role of solvent-detergent treated plasma (Octaplas) in acute thrombotic thrombocytopenic purpura. *Vox Sang* 2000;78(suppl 1):abstract 0043.
- 40 Stanworth SJ, Hyde CJ, Murphy MF: Evidence for indications of fresh frozen plasma. *Transfus Clin Biol* 2007;14:551–556.
- 41 Flesland O, Jorgensen J, Krusius T, Säfwen J, Gudmundson S: Haemovigilance in the Nordic countries. *Haematologica* 2005;90:135.
- 42 Hofer C, Genser D, Priebe B, Steif S: Hämovigilanz-Jahresbericht 2005. 2006:1–42. www.goeg.at/media/download/berichte/HaemJB_2005_Endbericht.pdf.
- 43 Genser D, Hofer C, Steif S: Hämovigilanz-Jahresbericht 2003. 2004. www.goeg.at/media/download/berichte/HaemJB_2003.pdf.
- 44 Hofer C, Genser D, Steif S: Hämovigilanz-Jahresbericht 2004. 2005. www.goeg.at/media/download/berichte/HaemJB_2004.pdf.
- 45 Priebe B, Hofer C, Genser D, Gollmer A: Hämovigilanz-Jahresbericht 2006. 2007. www.goeg.at/media/download/berichte/Haemovigilanz_Jahresbericht_2006.pdf.
- 46 Brunskill SJ, Tusold A, Benjamin S, Stanworth SJ, Murphy MF: A systematic review of randomized controlled trials for plasma exchange in the treatment of thrombotic thrombocytopenic purpura. *Transfus Med* 2007;17:17–35.
- 47 Barz D: Detection of antigen structures in blood cells in various prepared plasma transfusions. *Anaesthesiol Reanim* 1994;19:155–158.
- 48 Lefevre H, Walther-Wenke G, Burkhard J: Leukozytendepletion. *Bundesgesundheitsbl Gesundheitsforsch Gesundheitschutz* 1999;42:121–131.
- 49 Barz D, Kentouche K, Zintl F, Göhler T, Budde U: Treatment with solvent detergent (SD) treated plasma is efficacious and well tolerated in thrombotic thrombocytopenic purpura (TTP) due to congenital von Willebrand factor-cleaving protease (VWF-DP)-deficiency. *Vox Sang* 2002;83:99.

- 50 Yarranton H, Cohen H, Pavord SR, Benjamin S, Hagger D, Machin SJ: Venous thromboembolism associated with the management of acute thrombotic thrombocytopenic purpura. *Br J Haematol* 2003;121:778–785.
- 51 Beeck H, Hellstern P: In vitro characterization of solvent/detergent-treated human plasma and of quarantine fresh frozen plasma. *Vox Sang* 1998;74:219–223.
- 52 Hellstern P: Solvent/detergent-treated plasma: composition, efficacy, and safety. *Curr Opin Hematol* 2004;11:346–350.
- 53 Hellstern P, Haubelt H: Manufacture and composition of fresh frozen plasma and virus-inactivated therapeutic plasma preparations: correlation between composition and therapeutic efficacy. *Thromb Res* 2002;107(suppl 1):S3–S8.
- 54 Kreil TR, Berting A, Kistner O, Kindermann J: West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data. *Transfusion* 2003;43:1023–1028.
- 55 Rock G, Clark B, Sutton D: The Canadian Apheresis Registry. *Transfus Apher Sci* 2003;29:167–177.
- 56 Popovsky MA: Transfusion and the lung: circulatory overload and acute lung injury. *Vox Sang* 2004;87:62–65.
- 57 Sachs UJ, Kauschat D, Bein G: White blood cell-reactive antibodies are undetectable in solvent/detergent plasma. *Transfusion* 2005;45:1628–1631.