Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data

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Introduction

Studies from different clinical settings including cardiac surgery and postpartum haemorrhage (PPH) have indicated that low fibrinogen levels are associated with an increased risk of bleeding (1–6). Fibrinogen deficiency can arise from congenital defects or acquired hypofibrinogenemia. Blood loss, for example during surgery, following trauma or as a result of PPH, results in coagu- lupathy and reduced fibrinogen levels (7–9). Massive transfusion is frequently used to treat haemorrhage, but can itself result in dilutional coagulopathy (10–12). Indeed, fibrinogen is the first coagulation factor to decrease to a critically low level during major blood loss and replacement with red blood cells (RBCs) (10). An additional cause of hypofibrinogenemia is hyperfibri- nolysis, which can follow severe shock, major tissue trauma, out- of-hospital cardiac arrest or acidosis (13–15). Finally, reduced fibrinogen levels can be a consequence of impaired fibrinogen synthesis, which can result from hypothermia or impaired liver function (16–18).

Traditionally, fibrinogen deficits have been treated using transfusion of cryoprecipitate or therapeutic plasma (e.g. fresh frozen plasma [FFP]) (7). An alternative therapy is the administration of fibrinogen concentrate. Haemocomplettan® P (CSL Behring, Marburg, Germany; also marketed under the trade name RiaSTAP®) is a plasma-derived, pasteurised and lyophilised human fibrinogen concentrate manufactured from pooled plasma donations collected in the USA and several countries within Europe, excluding the UK, and was introduced into the European market in 1986. Haemocomplettan P is licensed in a number of countries for therapy and prophylaxis of haemorrhagic diathesis in: congenital hypo-, dys-, or afibrinogenemia and acquired hypofibrinogenae- mia resulting from increased loss, increased intravascular con- sumption, e.g. as a result of disseminated intravascular coagulation (DIC) or of hyperfibrinolysis, and in disorders of synthesis in cases of severe liver parenchyma damage (7, 19, 20). Under the trade name RiaSTAP, fibrinogen concentrate is also licensed in a number of countries for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including...
afibrinogenaemia and hypofibrinogenaemia (7, 21, 22). RiaSTAP is not indicated for dysfibrinogenaemia. Solomon et al. provide a comprehensive summary of the licensing information for Haemocomplettan P/RiaSTAP (20).

A number of studies have found that treatment with fibrinogen concentrate, either as a standard dose or guided by thromboelastometry measurements, reduced both transfusion requirements and blood loss in the perioperative setting (23–29). In particular, the efficacy of fibrinogen concentrate has been demonstrated in clinical trials with patients undergoing aortic replacement surgery (30) and complex cardiac surgery (31), in retrospective analyses of trauma patients (32, 33), and in a case series of patients with PPH (34). Fibrinogen concentrate administration has been described as effective and safe in surgical and trauma patients by several systematic reviews (35–37). A Cochrane review of fibrinogen concentrate in bleeding patients stated there was not enough data to make safety conclusions, but did note that no harm or adverse events caused by treatment with fibrinogen concentrate could be identified (38). Current European guidelines for the management of perioperative bleeding recommend the use of fibrinogen concentrate if significant bleeding is accompanied by at least suspected low fibrinogen levels and/or function, and suggest including fibrinogen concentrate in goal-directed treatment algorithms (39).

One of the concerns associated with administering a coagulation factor replacement product is the perceived risk of triggering a thromboembolic event (TEE). Post-hoc analysis of a randomised clinical trial has demonstrated that although plasma fibrinogen concentration and the quality of the fibrin-based clot were elevated soon after administration of fibrinogen concentrate, the effects were short-lived, with no differences versus control seen at 1–9 days following treatment (40). This finding suggests a low potential for thromboembolic events and is supported by animal models and safety reports; no evidence of thrombus formation was observed in an animal model of venous stasis, and a previous analysis of the pharmacovigilance database demonstrated that the incidence of thrombotic events possibly related to fibrinogen concentrate was approximately 3.5 per 10^6 treatment episodes (41). A study of fibrinogen concentrate in pigs also found no signs of hypercoagulability or thromboembolism during the 6 hours (h) following doses as high as 600 mg/kg body weight (approximately 42 g in a 70 kg patient) (42).

This descriptive study summarises a large pharmacovigilance dataset for fibrinogen concentrate (Haemocomplettan P/RiaSTAP) from 1986 to 2013 and reviews key safety reports from the recent literature. The intent is to evaluate the safety profile of fibrinogen concentrate, including an assessment of its thrombogenic potential, through the assessment of clinical practice data and published literature.

Materials and methods

Pharmacovigilance adverse drug reaction (ADR) reports were compiled from January 1, 1986 to December 3, 2013. These data were collected as part of on-going CSL Behring routine pharmacovigilance, and included spontaneous reports, reports from post marketing trials, reports from regulatory agencies and cases identified from a review of the worldwide scientific literature (all spontaneous reports were assumed to be ADRs). For each ADR report, the year, country of origin, patient age and sex, indication, fibrinogen concentrate dose, concomitant products, and manifestations and outcome of the ADR were recorded if available. Wherever possible, a narrative description of the ADR was obtained. Where relevant information was missing from the initial report, the reporting source was queried for further clarification; however, the information was not always available. ADRs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1, and the event was classified as serious vs non-serious according to regulatory definition (a serious event was one which resulted in death, was life-threatening, required hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was a medically important event).

The cumulative quantity of fibrinogen concentrate distributed during the study period was established from CSL Behring commercial records. As the actual total number of patients who received fibrinogen concentrate is not known, patient exposure is presented as number of estimated 4 g standard doses based on the units distributed. The figure of 4 g was calculated based on the average total doses reported in the clinical studies retrieved in the literature review (17, 25–28, 30, 43–47). The reporting rate of cases involving ADRs is given both to the nearest 100 g and to the nearest 100 standard doses.

Standardised MedDRA Queries (SMQs), High Level Group Terms (HLGT), High Level Terms (HLT) and Preferred Terms (PT) within the MedDRA dictionary were used as needed to identify events of special interest (important identified and potential risks) for analysis as follows:

- Anaphylaxis and hypersensitivity/allergic reactions were identified using MedDRA SMQ anaphylactic reactions (narrow) and SMQ hypersensitivity (narrow).
- Thromboembolic complications were identified using MedDRA SMQ embolic and thrombotic events.
- Suspicion of virus transmission was identified using HLGT viral infectious disorders, HLTT infectious transmissions, HLTV virus identification and serology, PT viraemia and PT viral sepsis.

Once identified, these cases were not reviewed to confirm that they met case definitions. The reporting rates of MedDRA PTs in cases which did not include events of special interest (important identified and potential risks) were assessed in all remaining cases.

Literature review

A literature search was conducted using MEDLINE (PubMed) with the objective of identifying original, English language articles published between January 1, 1986 and December 3, 2013, which reported on clinical studies of Haemocomplettan P/RiaSTAP in bleeding patients. The following search terms were used:
The clinical study subjects, authors, methods, and time periods were examined to avoid inclusion of redundant data from multiple reports. Only studies evaluating Haemocomplettan P/RiaSTAP were included in the review. The following data were extracted from the study reports: number and age of subjects, type of fibrinogen deficiency, indication for fibrinogen concentrate infusion, treatment regimen, and the occurrence of adverse events (AEs). Only studies reporting safety data were included, and all AEs reported in the clinical studies were included regardless of whether or not a relationship to fibrinogen concentrate was established.

Results
Pharmacovigilance
Baseline characteristics

Between January 1, 1986 and December 3, 2013, a total of 383 events in 106 cases were reported. The age range of the patients was 15 days to 81 years, and the mean age was 38.0 ± 21.7 years. The gender ratio was approximately even (49 male vs 47 female, gender was not recorded in 10 cases); four of the females were recorded as pregnant. A total of 16 fatal cases were reported. The reasons for fibrinogen concentrate administration were varied, including both congenital and acquired fibrinogen deficiency (e.g. due to haemorrhage relating to surgery, trauma, obstetrics, or liver transplantation). Fifty-five cases (51.9 %) involved acquired fibrinogen deficiency, and 39 cases (36.8 %) involved congenital fibrinogen deficiency. In 12 cases (11.3 %) the type of fibrinogen deficiency was not recorded.

Nature and rate of adverse drug reactions

During the reporting period 2,611,294 g of fibrinogen concentrate were distributed, corresponding to 652,824 standard doses of 4 g each. Fibrinogen concentrate was distributed across Europe, Africa, Australia, Canada, Iran, Israel, Saudi Arabia, South America (e.g. Brazil and Argentina), Turkey, and the US, and has a high per capita consumption in countries with a labelled indication that includes both congenital and acquired fibrinogen deficiency, e.g. Germany, Austria, Switzerland, and the Netherlands.

The 106 reported cases corresponded to approximately one case per 24,600 g fibrinogen concentrate distributed or for every 6,200 standard doses administered. Of these, 81 cases were classified as serious according to regulatory definition, corresponding to one case reported per 32,200 g fibrinogen concentrate distributed for every 8,000 standard doses administered. Cases which included events considered to be important risks (anaphylaxis and hypersensitivity/allergic reactions and thromboembolic complications) or potential risks (suspicion of virus transmission) were identified.

Anaphylaxis and hypersensitivity/allergic reaction

A total of 20 cases of the 106 (18.9 %) with 40 possible hypersensitivity reaction events were reported; this is approximately one case reported per 130,600 g fibrinogen concentrate distributed or for every 32,600 standard doses of 4 g each. Possible hypersensitivity reactions were reported in 11 male patients and eight female patients (gender was not recorded in one case), with a mean age of 38.4 ± 26.3 years and an age range of 3–81 years. Eight of the reported cases (40.0 %) were in acquired fibrinogen deficiency, whilst 10 (50.0 %) were in congenital cases (not recorded in two cases [10.0 %]). A range of reactions were recorded, with the most common being hypersensitivity (eight cases), anaphylactic reaction (five cases) and shock (five cases). A fatal outcome was reported in five cases; however, only one of these cases reported that the death was associated with an anaphylactic reaction. The other four deaths were not related to an allergic reaction. Causes of death in these cases were sepsis, cerebral oedema, intraoperative bleeding and cardiac failure. Use of concomitant products was recorded in 10 cases (50.0 %). In particular this included therapeutic plasma (five cases) and RBCs (five cases).

Thromboembolic complications

A total of 28 of the 106 cases (26.4 %) with 45 possible TEEs were reported through December 3, 2013 (Table 1 and Table 2); this is approximately one case reported per 93,300 g fibrinogen concentrate distributed or for every 23,300 standard doses of 4 g each. The patients’ mean age was 37.4 ± 21.2 years, and the age range was 15 days to 76 years; ten of the patients were male and 13 female (gender was not recorded in five cases). The reported TEEs included myocardial infarction, pulmonary embolism, deep-vein thrombosis, arterial thrombosis and cerebral infarction. Six of the 28 reports were from one literature article (48). Of the 28 cases reported, eight had a fatal outcome. Three deaths were not related to the TEEs and the causes of death were liver failure, sepsis and systemic inflammatory response syndrome. In the remaining cases additional risk factors existed that provided alternative causes for the TEE (e.g. concomitant application of coagulation factors that increase thrombin generation, platelets, RBCs, etc., or factors that may have increased the risk of TEE, such as history of previous TEE, or concomitant diseases, such as end stage liver failure and DIC).

Over half of the reported TEE cases involved acquired fibrinogen deficiency (16 cases, 57.1 %, Table 1); the remaining 12 cases (42.9 %) were congenital (Table 2). From the available information, slightly more cases were reported in female than male patients for the acquired fibrinogen deficiency cases (six female vs five male, gender not reported in five cases) and the congenital cases (seven female and five male cases). The age range was 15 days to 76 years for the acquired fibrinogen deficiency patients, and 11 to 48 years for the congenital fibrinogen deficiency patients. All eight reported fatal cases were in acquired fibrinogen deficiency patients. Among the eight cases with fatal outcomes, three deaths were not related to TEEs. Other confounding factors (e.g. concomitant diseases and medications) provided alternative explanations for TEE development in the remaining five fatal cases.
Suspicion of virus transmission
A total of 21 of the 106 cases with 34 possible events of transmissions of infectious agents were reported; this is approximately one case reported per 124,300 g fibrinogen concentrate distributed or for every 31,000 standard doses of 4 g each. These comprised 19.8% of the total cases, and none of these cases had a fatal outcome. The mean age was 46.6 ± 16.4 years, and the age range was 21–77 years; 11 of the patients were male and nine female (gender

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Indication</th>
<th>Event (Preferred Term)</th>
<th>Concomitant and co-suspect drugs</th>
<th>Patient age (years)</th>
<th>Medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coagulation parameters (fibrinogen) low</td>
<td>1. Pulmonary embolism* 2. Intracardiac thrombus*</td>
<td>--</td>
<td>16</td>
<td>Relevant history: celiac-induced liver failure, liver transplantation, chronic liver graft failure, failed liver re-transplant Concomitant disease: liver re-transplantation</td>
</tr>
<tr>
<td>2</td>
<td>DIC</td>
<td>1. Pulmonary embolism</td>
<td>--</td>
<td>NI</td>
<td>Relevant history: circulatory arrest, caesarean section, amniotic fluid embolus Concomitant diseases: DIC</td>
</tr>
<tr>
<td>3</td>
<td>General surgery</td>
<td>1. Acute myocardial infarction</td>
<td>--</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>4</td>
<td>Gynaecological surgery</td>
<td>1. Acute myocardial infarction*</td>
<td>FFP</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>5</td>
<td>Haemorrhagic shock</td>
<td>1. DIC</td>
<td>Kybernin P, Beriplex P/N, Novo Seven, FFP, RBC</td>
<td>33</td>
<td>Concomitant diseases: haemorrhagic shock, uterine bleeding (postpartum)</td>
</tr>
<tr>
<td>6</td>
<td>Heart surgery</td>
<td>1. Acute myocardial infarction*</td>
<td>PCC, FFP</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>7</td>
<td>Improvement of coagulation, Haemostasis</td>
<td>1. Subclavian artery thrombosis* 2. Vena cava thrombosis*</td>
<td>AT III, PCC, Platelets, Protamine sulphate, NovoSeven, Packed RBC, FFP</td>
<td>0.04</td>
<td>Concomitant diseases: Ross procedure, replacement of a partially occluded pulmonalis graft, congenital aortic stenosis, left ventricular fibroelastosis</td>
</tr>
<tr>
<td>8</td>
<td>NI</td>
<td>1. Myocardial infarction*</td>
<td>Actilyse, Aspirin, Plavix, Cloxane, Prothromplex, Concor, Nitroderm</td>
<td>72</td>
<td>Relevant history: disembolism of aorta, acute myocardial infarction (unspecified) Concomitant disease: epistaxis</td>
</tr>
<tr>
<td>9</td>
<td>Procedural bleeding</td>
<td>1. Hepatic artery thrombosis</td>
<td>Antivirals, Nadolol, Spironolactone, Tacrolimus, Mycophenolate</td>
<td>57</td>
<td>Concomitant diseases: liver transplant, alcoholic liver cirrhosis, hepatitis B virus infection, hepatocellular carcinoma, obesity</td>
</tr>
<tr>
<td>10</td>
<td>Severe hypofibrinogenaemia</td>
<td>1. Thrombotic microangiopathy 2. Thrombosis</td>
<td>Trasylol</td>
<td>69</td>
<td>Concomitant diseases: acute monocytic leukaemia, cutaneous haematomas, sustained haemorrhage from venous puncture sites, INR 2.51, prolonged activated partial thromboplastin time, prolonged thrombin time, increased D dimer levels</td>
</tr>
<tr>
<td>11</td>
<td>Spontaneous bleeding</td>
<td>1. Renal embolism 2. Pulmonary embolism</td>
<td>PCC</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>12</td>
<td>Trauma surgery</td>
<td>1. Pulmonary embolism*</td>
<td>FFP</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>13</td>
<td>Vascular surgery</td>
<td>1. Cerebral infarction*</td>
<td>FFP</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>14</td>
<td>Liver transplantation</td>
<td>1. Hepatic artery thrombosis</td>
<td>Platelets, Remifentanile, Cisatracure, Amoxicillin/Clavulanic, ACE inhibitor</td>
<td>55</td>
<td>Relevant history: colectomy, septic arthritis Concomitant disease: alcoholic liver cirrhosis, hypertension</td>
</tr>
</tbody>
</table>
### Table 1: Continued.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Indication</th>
<th>Event (Preferred Term)</th>
<th>Concomitant and co-suspect drugs</th>
<th>Patient age (years)</th>
<th>Medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Haemostasis</td>
<td>1. Thrombosis in device 2. Thrombosis in device</td>
<td>Mannitol, Heparin, Cefazolin, Normosol, KCl in 5% dextrose and 0.225% NaCl₂, Sodium bicarbonate, MgSO₄, Protamine sulfate</td>
<td>54</td>
<td>Relevant history: mitral stenosis, bicuspid aortic valve with aortic root aneurysm, anomalous left upper pulmonary vein, mitral valve replaced with bioprosthesis, valve-sparing root replacement, anomalous pulmonary vein re-implanted to left atrial appendage Risk factor: arterial/venous catheters Concomitant disease: CPB</td>
</tr>
</tbody>
</table>

ACE: angiotensin converting enzyme; AT III: antithrombin III; CPB: cardiopulmonary bypass; DIC: disseminated intravascular coagulation; FFP: fresh frozen plasma; INR: international normalised ratio; NI: no information given; PCC: prothrombin complex concentrate; RBC: red blood cells. *Event was fatal.

### Table 2: Reported cases involving thromboembolic complications in congenital fibrinogen deficiency patients.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Indication</th>
<th>Event (Preferred Term)</th>
<th>Concomitant and co-suspect drugs</th>
<th>Patient age (years)</th>
<th>Medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Afibrinogenaemia</td>
<td>1. Deep-vein thrombosis 2. Deep-vein thrombosis</td>
<td>Valoron, Temgesic, Steroids, Endoxan, Antibiotics</td>
<td>32</td>
<td>Relevant history: drug abuse, parenchymal haemorrhage, hemianopsia, lung embolism/infarction pneumonia, partial amputation, haemorrhage right lower leg Concomitant diseases: mediastinal haemorrhage, pain in toe, vasculitis, reduced general condition, cyst of thyroid, dry gangrene toe, respiration abnormal, central venous catheterisation, heart rate increased, depression</td>
</tr>
<tr>
<td>3</td>
<td>Afibrinogenaemia</td>
<td>1. Retinal vein thrombosis</td>
<td>–</td>
<td>41</td>
<td>Relevant history: thromboembolic event (brain), hepatitis C virus</td>
</tr>
<tr>
<td>4</td>
<td>Afibrinogenaemia, Multiple haemorrhagic events</td>
<td>1. Arterial thrombosis</td>
<td>Clottagen</td>
<td>23</td>
<td>NI</td>
</tr>
<tr>
<td>5</td>
<td>Afibrinogenaemia</td>
<td>1. Peripheral artery thrombosis</td>
<td>Heparin, Aspirin, Lepirudin</td>
<td>44</td>
<td>Relevant history: cerebral haemorrhage</td>
</tr>
<tr>
<td>7</td>
<td>Afibrinogenaemia, Spontaneous extradural and subdural haemorrhage</td>
<td>1. Pulmonary embolism</td>
<td>–</td>
<td>32</td>
<td>Relevant history: occasional ecchymoses Concomitant diseases: frontal headache, flu-like symptoms, vascular collapse, INR increased, APTT increased</td>
</tr>
<tr>
<td>8</td>
<td>Afibrinogenaemia</td>
<td>1. Pulmonary embolism</td>
<td>–</td>
<td>12</td>
<td>Relevant history: central venous lines (port catheter) Concomitant disease: septicaemia</td>
</tr>
</tbody>
</table>
was not recorded in one case). Fifteen cases (71.4%) involved acquired fibrinogen deficiency, and two cases (9.5%) involved congenital fibrinogen deficiency. In four cases the type of fibrinogen deficiency was not recorded. The suspected virus transmissions included 15 suspected cases related to hepatitis C (including one patient with a suspected co-infection with hepatitis A; however, hepatitis A infection was not confirmed) and five suspected cases related to hepatitis B (including one patient with a suspected co-infection with HIV; however, HIV infection was not confirmed).

In all the reports concerning suspected virus transmission (except one with insufficient data), a causal relationship to the product was assessed as unlikely due to an alternative explanation and/or non-reactive polymerase chain reaction (PCR) tests for the concerned batches and/or related plasma pools for fractionation. Fourteen of these cases had no data regarding the respective virus infection prior to treatment; therefore an assessment as to whether the infection occurred after fibrinogen concentrate administration or previous to this treatment is not possible. In addition, 17 of the patients (81.0%) received allogeneic blood products concomitantly. In one patient a cytomegalovirus infection was diagnosed; this was most probably a re-activation of a previous infection due to immunosuppressant treatment after organ transplantation.

Other reported events
Thirty-seven cases were not classified as anaphylactic, allergic, thromboembolic, or virus-related. When assessing these events by the MedDRA System Organ Class (SOC), the most common type of events were general disorders and administration site conditions (21 cases), respiratory, thoracic and mediastinal disorders (10 cases), injury, poisoning and procedural complications (six cases) and vascular disorders (six cases). The most common MedDRA PTs reported (in three or more cases) were pyrexia, chills, drug ineffective, nausea, exposure during pregnancy, and tachycardia (Figure 1). Furthermore, a lack of drug effect was reported in four cases, in addition to a lack of effect in an unapproved indication reported in two cases.

Four reports of suspected transfusion-related acute lung injury (TRALI) were received (one in conjunction with an allergic event and one in conjunction with a TEE); however, in each case the patient also received RBCs and/or FFP.

Literature review
Haemocomplettan P/RiaSTAP has been administered in 20 clinical studies that reported safety results between January 1, 1986 and
Three of these papers were excluded from the literature search results as they described cases that are included in the pharmacovigilance results (Kreuz et al. [49], Weiss et al. [48], and Gollop et al. [50]). The results of the remaining 17 studies are summarised in ▶ Table 3.

Fibrinogen was administered to 899 patients for a range of indications covering both congenital and acquired fibrinogen deficiency. Ten of the studies were prospective (26–28, 30, 45–47, 51–53) and seven were retrospective (17, 23, 25, 43, 44, 54, 55). The number of patients in each study ranged from five to 294. Both adult and paediatric patients were included in three studies, one study was exclusively in children, the rest included patients ≥ 16 years old.

Seven of the studies reported that no AEs were observed (23, 26, 43–46, 54).

Company-sponsored studies

A prospective study to evaluate the efficacy and safety of Haemocomplettan P treatment following major aortic replacement surgery was carried out by Rahe-Meyer et al. (30). During this clinical trial similar proportions of subjects reported AEs in the treatment group as in the control group (83% vs 84%, respectively), leading the authors to conclude there was no observed safety concern (30).

Manco-Johnson et al. (52) describe an open-label, multicentre, non-controlled, prospective study to investigate the pharmacokinetic properties and safety of Haemocomplettan P in subjects with congenital afibrinogenemia. Subjects were observed following treatment administration and mild AEs were observed in two subjects (described in ▶ Table 3), which were not considered related to the study drug by the authors (three of the four AEs reported did not occur until at least nine days after fibrinogen concentrate infusion) (52).

Studies supported by the company

Prospective studies to evaluate the efficacy of Haemocomplettan P following aortic surgery were carried out by Rahe-Meyer et al. (27, 28). The only AEs reported in these pilot studies were one subject of the 10 receiving fibrinogen concentrate developing postoperative atrial fibrillation (compared to one subject of the five receiving conventional allogeneic blood products-based haemostatic management) (27), and one subject of the six receiving fibrinogen concentrate requiring prolonged respiratory assistance (compared to five of 12 subjects in a retrospective analysis of patients receiving allogeneic blood products) (28).

Tanaka et al. (53) investigated transfusion requirements and haematologic variables following treatment with RiaSTAP (10 subjects) or platelets (control group; 10 subjects). There was no significant difference observed between the fibrinogen concentrate and control groups for the incidence of reexploration for bleeding (10% vs 20%, respectively), acute myocardial infarction (0% vs 10%), or pulmonary oedema (30% vs 50%).

Kreuz et al. (51) describes an open-label, multicentre, non-controlled study to investigate the pharmacokinetic properties, safety and tolerability of Haemocomplettan P in subjects with congenital afibrinogenemia or severe hypofibrinogenemia. Following treatment administration, mild to moderate AEs were observed in two subjects (described in ▶ Table 3). These AEs were reported as possibly related to the administration of fibrinogen concentrate, and resolved within 6 h of treatment (51).

Independent studies

Non-controlled retrospective studies

Weinkove and Rangarajan (17) described a retrospective review of 30 adult patients assessing the safety and efficacy of Haemocomplettan P for acquired fibrinogen deficiency. Four cases of arterial
### Table 3: Clinical studies of Haemocomplettan P/RiaSTAP with safety data.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>No. subjects receiving fibrinogen concentrate</th>
<th>Age (years)*</th>
<th>Indication</th>
<th>Dose (g)*</th>
<th>Adverse events reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital fibrinogen deficiency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kreuz et al. (51)</td>
<td>Prospective non-controlled study (supported by CSL Behring)</td>
<td>5</td>
<td>(22–23)</td>
<td>A fibrinogenemia, hypofibrinogenemia</td>
<td>69–71 mg/kg</td>
<td>Elevated body temperature and dyspnoea in one patient; dizziness and elevated blood pressure in one patient</td>
</tr>
<tr>
<td>Manco-Johnson et al. (52)</td>
<td>Prospective company-sponsored non-controlled study</td>
<td>14</td>
<td>Mean 30 (8–61)</td>
<td>A fibrinogenemia</td>
<td>77 mg/kg</td>
<td>Four events (headache, gastroesophageal reflux disease, pain, epistaxis) in two patients</td>
</tr>
<tr>
<td><strong>Acquired fibrinogen deficiency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haas et al. (54)</td>
<td>Retrospective non-controlled analysis</td>
<td>9</td>
<td>1 (0.7–1.8)</td>
<td>Craniosynostosis surgery</td>
<td>76 mg/kg (IQR 67–100 mg/kg)</td>
<td>None reported</td>
</tr>
<tr>
<td>Danés et al. (43)</td>
<td>Retrospective non-controlled analysis</td>
<td>69</td>
<td>Mean 52 (1–89)</td>
<td>Surgery/trauma; sepsis; upper gastrointestinal tract haemorrhage; gynaecological diseases; haematological malignancies; liver transplantation; hepatic insufficiency; other</td>
<td>3.52 g (0.5–8 g)</td>
<td>None reported</td>
</tr>
<tr>
<td>Weinkove and Rangarajan (17)</td>
<td>Retrospective non-controlled analysis</td>
<td>30</td>
<td>42 (17–71)</td>
<td>Placental abruption; massive blood loss and transfusion; liver failure; postcardiac surgery; other</td>
<td>6 g (2–35 g)</td>
<td>Ischaemic cerebrovascular accidents in three patients; myocardial infarction in one patient</td>
</tr>
<tr>
<td>Fenger-Eriksen et al. (25)</td>
<td>Retrospective non-controlled analysis</td>
<td>43</td>
<td>Mean 49.5 (0.1–76)</td>
<td>Surgery and massive haemorrhage</td>
<td>2 g (1–5 g) in adults; 0.35 g (0.2–0.5 g) in children</td>
<td>Jitter and snoring respiration in one patient; shivering in one patient; death (cause unspecified) in one patient</td>
</tr>
<tr>
<td>Rahe-Meyer et al. (27)</td>
<td>Prospective controlled study (supported by CSL Behring)</td>
<td>10</td>
<td>Mean 57 (25–76)</td>
<td>Aortic valve operation and ascending aorta replacement</td>
<td>Mean 5.7 g (SD 0.7 g)</td>
<td>Postoperative atrial fibrillation in one patient</td>
</tr>
<tr>
<td>Karlsson et al. (26)</td>
<td>Prospective randomised controlled study (supported by CSL Behring)</td>
<td>10</td>
<td>Mean 66 ± 9</td>
<td>Coronary artery bypass</td>
<td>2 g</td>
<td>None reported†</td>
</tr>
<tr>
<td>Rahe-Meyer et al. (28)</td>
<td>Prospective study (supported by CSL Behring)</td>
<td>6</td>
<td>Mean 56.8 ± 8.9</td>
<td>Aortic aneurysm operation</td>
<td>Mean 7.8 g (SD 2.7 g)</td>
<td>Prolonged respiratory assistance in one patient</td>
</tr>
<tr>
<td>Solomon et al. (23)</td>
<td>Retrospective non-controlled analysis</td>
<td>39</td>
<td>Mean 58 (25–78)</td>
<td>Cardiopulmonary bypass</td>
<td>Mean 78 mg/kg (SD 20 mg/kg)</td>
<td>None reported</td>
</tr>
<tr>
<td>Thorarinsdottir et al. (44)</td>
<td>Retrospective non-controlled analysis</td>
<td>37</td>
<td>74 (23–87)</td>
<td>Severe haemorrhage following open heart, abdominal or obstetric/gynaecologic surgery; gastrointestinal haemorrhage</td>
<td>2 g (1–6 g)</td>
<td>None reported</td>
</tr>
<tr>
<td>Ahmed et al. (45)</td>
<td>Prospective data analysis</td>
<td>20</td>
<td>Mean 31</td>
<td>Obstetric haemorrhage</td>
<td>Mean 4 ± 0.8 g</td>
<td>None reported</td>
</tr>
<tr>
<td>Solomon et al. (46)</td>
<td>Prospective controlled cohort study (supported by CSL Behring)</td>
<td>10</td>
<td>66 (IQR 53–71)</td>
<td>Coronary artery bypass</td>
<td>6 g (4–6 g)</td>
<td>None reported</td>
</tr>
</tbody>
</table>
Solomon et al. 27 years of fibrinogen pharmacovigilance data

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ischaemic events were reported in this study, but none were considered related to fibrinogen treatment by the authors.

Fenger-Eriksen et al. (25) also carried out a retrospective review of the effects of Haemocomplettan P on laboratory and clinical outcome in adult and paediatric patients with acquired fibrinogen deficiency, and described three patients with AEs where a causal relationship to fibrinogen treatment could not be excluded: two non-serious AEs and one unknown event with a fatal outcome.

Cohort analysis

Bilecen et al. (47) carried out a prospective cohort analysis over four years, evaluating 264 subjects who received Haemocomplettan P during complex cardiac surgery, compared with the control group of 811 subjects who were not treated with fibrinogen concentrate. No difference was observed between the two groups in the occurrence of 30-day mortality, myocardial infarction, cerebrovascular accident/transient ischaemic attack, renal insufficiency/failure, or infections. This led the authors to conclude that fibrinogen administration carried no increased risk of clinical AEs.

Wafaisade et al. (55) also carried out a cohort analysis of 294 subjects from the Trauma Registry of the German Society for Trauma Surgery who had received Haemocomplettan P during initial care between emergency department arrival and intensive care unit admission (FC+ group) matched with 294 subjects who had not received the product (FC− group). Subjects in the FC+ group had lower mean 6-h mortality (10.5% compared to 16.7%, p=0.03), and longer mean time to death (7.5 days compared to 4.7 days, p=0.006). Concordantly, higher multiple organ failure rate (61.2% vs 49.0%, p=0.003) and higher thromboembolism occurrence (6.8% vs 3.4%, p=0.06) were observed in the FC+ group. No further information was provided regarding the TEEs observed in this study.

Discussion

This descriptive analysis of over 27 years of pharmacovigilance data indicates that the rate of ADRs reported following the administration of Haemocomplettan P/RiaSTAP across diverse clinical settings is low. In total 106 cases were reported, corresponding to a rate of one case per 24,600 g fibrinogen concentrate distributed or for every 6,200 standard doses of 4 g each.

The risk of triggering a TEE by administering fibrinogen concentrate appears to be low. In an earlier analysis of the pharmacovigilance database, Dickneite et al. identified nine cases of thrombosis possibly related to fibrinogen concentrate, and calculated an
incidence of approximately 3.5 events per 10^5 treatment episodes (41). The current analysis identified approximately 4.3 cases per 10^5 treatment episodes (calculated from 28 cases reporting a possible TEE, corresponding to one case for every 23,300 standard doses of 4 g each). This rate may appear slightly higher than that reported by Dickneite; however, in contrast to the Dickneite paper (which included only the TEs that were considered to be related to fibrinogen concentrate by the pharmacovigilance department), this analysis included all reported TEs, regardless of their relationship to fibrinogen concentrate. In most of the cases reported here, additional risk factors existed that may provide alternative causes for the TEE (e.g. concomitant application of other coagulation factors, pre-existing conditions, etc.). A low risk of TEE occurrence is further supported by Dickneite et al., who present the evaluation of the thrombogenic potential of fibrinogen concentrate in the long-established Wessler stasis model, assessed in rabbits receiving either 100 or 250 mg/kg fibrinogen concentrate (41). No evidence of thrombus formation during venous stasis was observed in any of the animals treated with fibrinogen concentrate, although the equivalent of 8 g and 20 g fibrinogen concentrate in an 80 kg bodyweight individual was administered.

With regard to virus transmission and to the techniques for virus inactivation applied to plasma-derived products, it is noteworthy that the production of Haemocomplettan P/RiaSTAP includes multiple precipitation/adsorption steps which have been demonstrated to reduce the risk of virus transmission in an additive manner: cryoprecipitation, Al(OH)_3 adsorption/glycine precipitation/Al(OH)_3 adsorption, heat treatment (+60°C for 20 h in an aqueous solution; “pasteurisation”), and two subsequent glycine precipitation steps (initial and main glycine precipitation steps) (56). In addition to the virus removal and/or inactivation measures applied during the production process, prevention of transfusion of blood-borne viruses also includes steps related to limiting the virus input to the human plasma used as source (57), including donor selection and screening of individual donations and plasma pools for specific markers of infection. In this review, 21 cases were identified involving suspected transmission of infectious agents; however, further analysis indicated that these cases were not likely to be associated with fibrinogen concentrate administration.

It is difficult to estimate whether ADRs like TEs were reported more frequently in congenital or in acquired fibrinogen deficiency. A number of factors indicate that the majority of fibrinogen concentrate is used in an acquired, rather than a congenital setting. Congenital fibrinogen disorders are extremely rare, estimated at one per million births (58, 59). Data from the UK Haemophilia Centre Doctors’ Organisation showed that as of March 31, 2012, only 175 fibrinogen deficiency and three hypofibrinogenaemia patients were registered in the UK, with 18 and 0, respectively, having received treatment during the previous 12 months (it is unclear how the distinction between fibrinogen deficiency and hypofibrinogenaemia was made). Accordingly, low levels of circulating fibrinogen are most commonly seen as a result of acquired disorders of coagulation in hospital settings. Additionally, the use of fibrinogen concentrate has increased, with 1,576,905 g distributed over the last five years alone, compared to 1,034,389 g distributed in the previous 22 years (41). It seems reasonable to attribute part of this increase to greater use in acquired fibrinogen deficiency settings. Taken together, the data gathered here and the low incidence of congenital fibrinogen deficiency, may indicate that the rate of reported ADRs is lower in acquired than congenital patients. A possible explanation is that patients with congenital fibrinogen deficiency may be at higher risk of TEs than those with acquired fibrinogen deficiency patients. This assumption is based on the observation that fibrinogen-deficient mice displayed a high rate of thrombus formation, with highly unstable thrombi, which embolised frequently (60). This is supported by an in vivo coagulation study using blood taken from an afibrinogenaemic patient, which demonstrated that thrombus formation was increased in the absence of fibrinogen (61). The thrombi formed in the absence of fibrinogen were larger and more loosely packed than those formed with fibrinogen, and the authors concluded that afibrinogenaemic patients could be at thrombotic risk. Additionally it should be noted that patients with congenital fibrinogen deficiency may require frequent treatment with fibrinogen concentrate and will be closely monitored, therefore, ADRs are more likely to be reported. In comparison, patients with acquired fibrinogen deficiency may only receive fibrinogen concentrate once in their lifetime, and are also likely to receive multiple drugs, making it less likely that an ADR would be attributed to fibrinogen concentrate and reported as such.

Alternative treatments for fibrinogen replacement focus on infusion of therapeutic plasma or cryoprecipitate. These approaches carry their own hazards, such as the risk when transfusing plasma of volume overload and its associated complications, including pulmonary dysfunction and renal insufficiency (62). In a recent study, therapeutic plasma transfusion was associated with transfusion-associated circulatory overload in nearly 5% of patients (63). Additionally, there is a confirmed risk of AEs such as allergic reactions, thrombotic events, TRALI when transfusing FFP, and renal toxicity associated with the use of cryoprecipitate and/or FFP (64–68). Indeed, cryoprecipitate has been withdrawn from a number of European countries due to safety concerns (69).

Analysis of the study results reported in the scientific literature indicated that the number of AEs reported was generally low, and no significant differences were observed when comparing with control groups (where available). However, a retrospective cohort analysis in trauma did observe increased multiple organ failure rate and thromboembolism occurrence in patients treated with fibrinogen compared to the control group receiving other therapies (55). This may be accounted for by a tendency of fibrinogen concentrate to be administered to patients with more severe trauma (as noted in the observation that the fibrinogen concentrate group was more coagulopathic and received more fibrinolitics included.
in the discussion following the publication [55]) (70). Additionally, the criteria used by the study for patient pair-matching may have selected for more severe cases in the fibrinogen group or cases in which fibrinogen concentrate was used as a “rescue therapy” (70).

In comparison, Warmuth et al. carried out a systematic review of prospective, controlled studies in which fibrinogen concentrate was used in the perioperative setting and in massive haemorrhage (35). Three studies were identified containing a total of 53 patients (26 receiving fibrinogen concentrate and 27 in the control group); 12% of the patients receiving fibrinogen concentrate experienced an AE in comparison to 44% of the control group. A Cochrane analysis of fibrinogen concentrate use in bleeding patients reviewed six randomised controlled trials, and concluded that AEs, especially thrombotic events, were reported as insignificant, with only very few cases reported in an overall small population; however, the analysis did note that the studies included were at high risk of bias and were underpowered to detect mortality, benefit or harm (38).

The results of the literature review supported the findings from the pharmacovigilance analysis, that fibrinogen administration results in a low rate of ADRs in general and TEE in particular, with no unusual patterns of AEs reported that aren’t described in the product label. Moreover, no allergic reactions or virus transmission events were identified during the literature review.

Post marketing pharmacovigilance can be a valuable tool for assessing safety data and identifying potential risks. However, it does have some limitations, such as the potential underreporting of ADRs. As reporting of ADRs during pharmacovigilance is a voluntary process, analysis of this data is limited by the willingness of the reporting source to report the case and supply enough detail for assessment of whether the drug contributed to an ADR. Although it is by its nature difficult to estimate, one review suggested that the level of underreporting could be as high as 90% (71). Additionally, over half of the events reported as part of this pharmacovigilance were considered to be serious ADRs, which may indicate that ADRs are more likely to be reported when they are assessed as serious. Of note, the disclaimer published on the European Medicines Agency’s ADR reports site alludes to the limitations of spontaneous reports by saying that the information on their website “does not reflect any confirmation of a potential link between the medicine and the observed effect” and that this information reflects “the reporter’s observations and opinions. A scientific assessment of a cause and effect relationship between a medicine and an effect is part of a continuous monitoring of the benefits and risks of a medicine; the assessment takes into account many other factors, such as the medical condition and the medical history of the patient.” Patients who received fibrinogen concentrate during perioperative bleeding are also likely to have received other therapies and to have multiple concomitant diseases, which might have contributed to the occurrence of any AEs observed during the postmarketing period. Therefore, it is difficult to establish whether or not a reported event was related to fibrinogen concentrate use. However, a key strength of post marketing data is the large scale and comprehensive coverage of the relevant patient population, as well as the opportunity to assess clinical practice data. An additional limitation of this study is that the cases retrieved from the pharmacovigilance database using SMQs and MedDRA terms were not reviewed to confirm that they met case definitions. Thus it is likely that the total number of cases in each event of special interest category is an underestimate of the actual number of cases in that category.

In summary, this assessment of clinical practice data from 27 years of pharmacovigilance indicates that treatment with fibrinogen concentrate carries a low risk of adverse drug reactions, and displays a promising safety profile.

Conflicts of interest
CS, AG, JY, and IP are employees of CSL Behring.

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